# STEREOCHEMISTRY

by

V. M. POTAPOV

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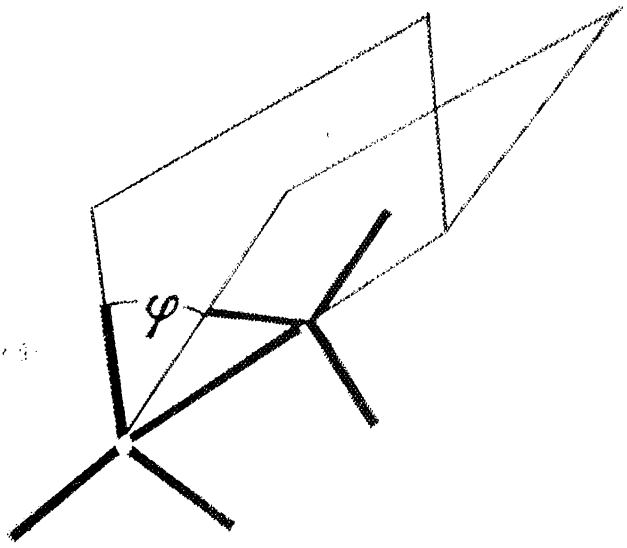
The book is devoted to one of the rapidly developing branches of knowledge—the stereochemistry of organic compounds. The discussion of the basic conceptions of this science is followed by a treatment of the stereochemistry of the principal classes of organic compounds: aliphatic, alicyclic, unsaturated, aromatic, and heterocyclic compounds.

Special chapters deal with the stereochemistry of nitrogen and other elements of Groups V and VI of Periodic System, and with the stereochemistry of complex compounds. Much emphasis is made in all chapters on conformational problems, the results of investigations of the spatial structure by means of modern physico-chemical methods, and on steric factors in reactions.

The book is a course of stereochemistry designed for students of chemistry and biochemistry at senior undergraduate and graduate level. It may also be used reading a special course of the theoretical foundations of organic chemistry. large body of original literature used main emphasis is made on works published in the sixties and seventies) makes it useful to post-graduates, teaching and a wide circle of research workers: chemists, biochemists, biophysicists and physicists acquainted with the foundations of organic chemistry.

Viktor Mikhailovich Potapov received his Doctor's degree from the Lomonosov State University (Moscow) in 1964. He is presently a Professor of Organic Chemistry at the Moscow State University. Dr. Potapov is primarily interested in the synthesis and spectropolarimetric investigation of optically active compounds.
He is a member of the editorial board of the journal *Analytical Chemistry* (USSR) and of the advisory boards of *Mir Publishers* and *Khimiya Publishers* (USSR).

Professor Potapov has authored over 200 publications, including the books *Foundations of Stereochemistry* (in co-authorship with A.P. Terentiev), *Nomenclature of Organic Compounds*, and *Chemical Information*, and also a number of textbooks and study aids for students of higher schools and colleges.

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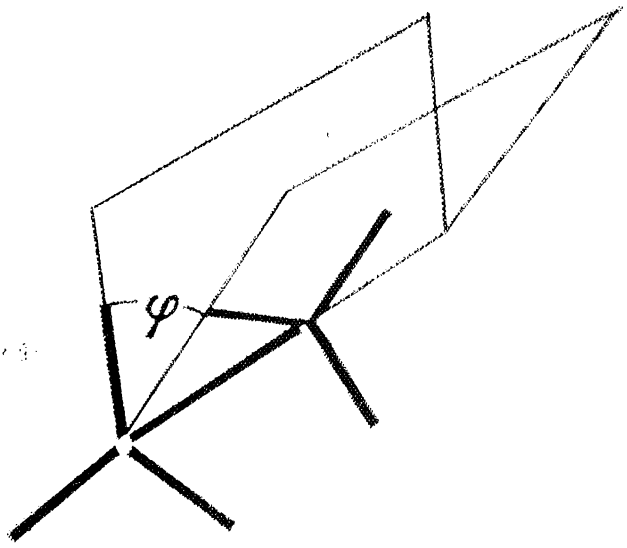


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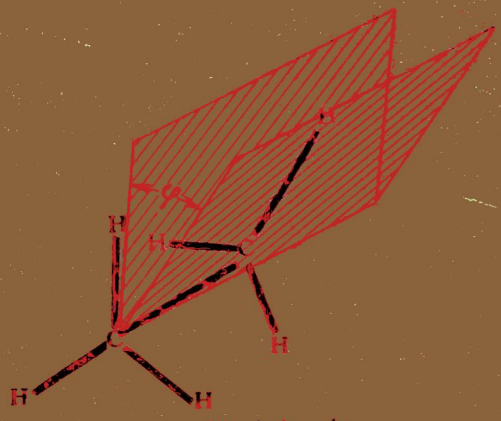
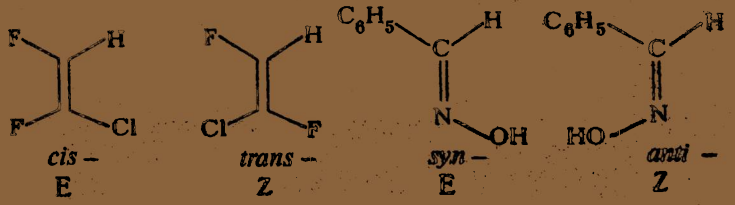
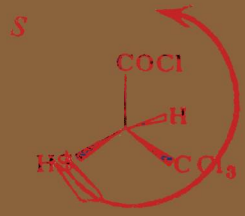


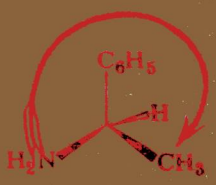

dihedral angle

methods of representation and designation of various




nomenclature of geometrical isomers



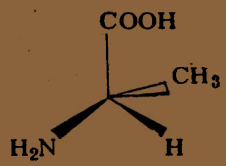

fall of priority

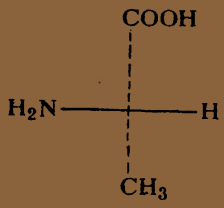
| | | | | |
|---|---|---|---|---|
| first set | S | C | C | H |
| second set | H | 3Cl | | – |

fall of priority

| | | | |
|---|---|---|---|
| N | C | C | H |
| 2H | 2C | 3H | – |

*R,S*-nomenclature of chiral structures



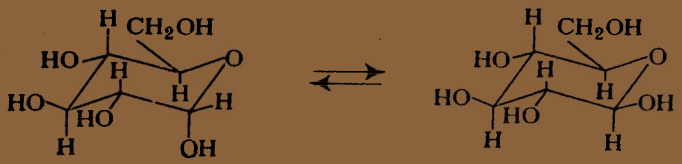




L-(+)-alanine

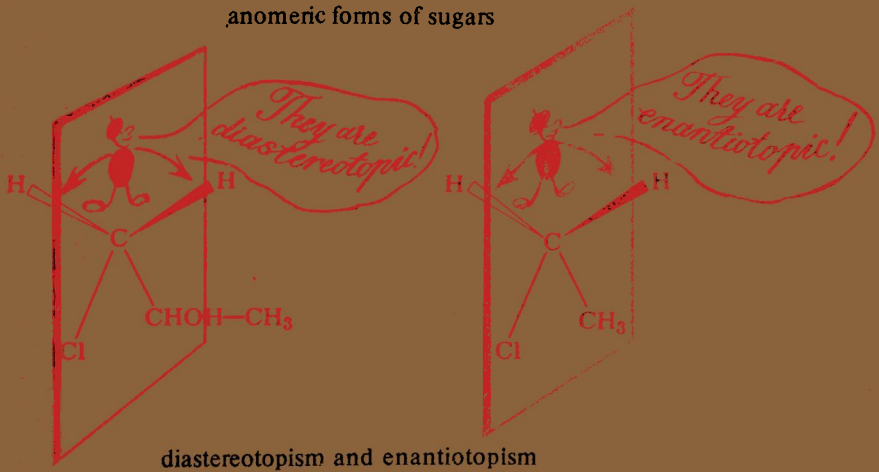
[*S*-(+)-alanine]

D,L–nomenclature of amino acids

conformations of 1,2-disubstituted compounds




anomeric forms of sugars




diastereotopism and enantiotopism

ИЗДАТЕЛЬСТВО МИР

В.М. ПОТАПОВ

# СТЕРЕОХИМИЯ

ИЗДАТЕЛЬСТВО
«ХИМИЯ»
МОСКВА

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by

V.M. POTAPOV

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Translated
from the Russian by
Artavaz Beknazarov

MIR
PUBLISHERS
MOSCOW

First published 1979
Revised from the 1976 Russian edition

На английском языке
© Издательство «Химия», 1976
© English translation, Mir Publishers, 1978

# Preface

More than 10 years have elapsed since the publication of "Foundations of Stereochemistry" by A.P. Terentiev and V.M. Potapov, which has since been used as a study aid by students at chemistry departments of universities, who major in organic chemistry and read a special course in stereochemistry. A large amount of new material has appeared for the last ten years and it became necessary to write a new textbook that would reflect the present state of development of stereochemistry.

The most important sections in classical stereochemistry were concerned with mirror-image (optical) isomerism. This was reflected in the content of "Foundations of Stereochemistry", in which much space was devoted to optically active substances. At present, main emphasis in stereochemistry is placed on the investigation of the fine details of the three-dimensional structure of molecules (conformational problems) by means of modern physical methods and also of the effect of the spatial structure on reactivity (dynamic stereochemistry). With the development of the spectropolarimetric method those sections which deal with optical activity have been fundamentally changed. All the changes have been reflected in the organization and content of this book.

First, the basic conceptions of stereochemistry are considered rather briefly but completely enough and at the present-day level of development. A special chapter is devoted to methods of preparing stereoisomers. Methods used to determine configurations are also described in a separate chapter. These chapters constitute, as it were, the first fundamental part in a study of stereochemistry.

The chapters of the second part are concerned with a detailed treatment of the stereochemistry of individual classes of organic compounds. In fact, these chapters are devoted to what might be called "organic chemistry in space", with a discussion of stereochemical problems characteristic of each class of compounds. These problems are discussed with no strict division into statics and dynamics, wide use being made throughout the text of conformational concepts and data supplied by modern physico-chemical methods of investigation. Teaching experience shows that such an order of presentation of the material more clearly reveals

the place and role of stereochemistry in modern organic chemistry, its significance to research workers engaged in the various segments of organic chemistry. There is a chapter dealing with the stereochemistry of complex compounds.

In selecting the literature cited, special emphasis was placed, as a rule, on the latest works, especially review articles. The book presents some historical background, but practically no references are made to the older literature; they can be found in "Foundations of Stereochemistry". A more or less comprehensive account of the history of development of stereochemistry had to be dispensed with since it would have required too much space at the expense of new material.

The author did his best to avoid giving too much space to his main area of investigation — the study of optically active substances by means of the spectropolarimetric method: though an important method of stereochemical investigation, it is nevertheless one of the many methods used currently in stereochemistry. Likewise, less attention (as compared with "Foundations of Stereochemistry") is paid to optical activity, since otherwise it would have been impossible to include new material.

The author hopes that the book, though addressed principally to students of chemistry, will also find readers among post-graduates, teachers, research workers engaged in the field of organic chemistry and the chemistry of complex compounds. The discussion of some of the problems may seem too concise and incomplete to the initiated, but it is impossible to cover, within a single book, the inexhaustible material of modern stereochemistry.

The author expresses his deep gratitude to Academician M.N. Kolossov, Professor K.A. Ogloblin and S.I. Yakimovich (Cand. Chem. Sc.) for detailed critical comments which were of great help in the preparation of the final version of the manuscript. The author will also be grateful to readers for comments, criticisms, and suggestions.

*V. M. Potapov*

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CHAPTER 1

# Basic Concepts of Stereochemistry

## 1.1. THE PLACE OF STEREOCHEMISTRY IN CHEMISTRY

Stereochemistry is a part of chemistry which is concerned with study of the spatial structure of molecules and of the influence of this structure on the physical and chemical properties of compounds and on the direction and rate of their reactions. Stereochemistry deals primarily with organic compounds; of inorganic compounds, mainly complex and inner-complex (chelate) compounds are studied.

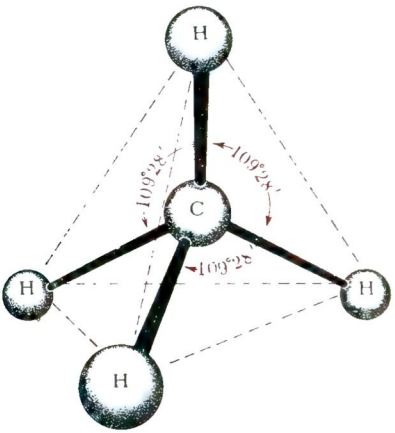
Until recently stereochemistry has been one of the most abstract theoretical areas of investigations. Now it has also assumed great practical importance. It has been found that the properties of polymers are substantially dependent on their spatial structure. This refers both to synthetic polymers (polystyrene, polypropylene, synthetic butadiene and isoprene rubbers) and to natural high-molecular-weight compounds, such as polysaccharides, proteins, nucleic acids. It is also known that the spatial three-dimensional structure exerts a great influence on the physiological properties of substances. What has been said above specifies the role of stereochemistry in the chemistry and technology of polymeric materials, in biochemistry and molecular biology, in pharmacology and medicine.

Stereochemical methods of investigation also help to solve the problems of theoretical organic and inorganic chemistry. The most familiar example in this field is the use of Walden inversion in the study of reaction mechanisms. The measurement of the magnitude of optical rotation by means of polarimeters is an important instrumental method of quantitative determination in a number of branches of industry (in the production of sugar, drugs, perfumes, etc.).

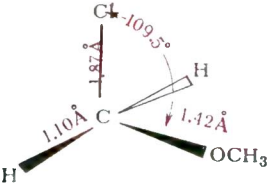
## 1.2. STEREOCHEMICAL FEATURES OF THE CARBON ATOM

The spatial structure of organic compounds is associated primarily with the specific stereochemical features of the carbon atom. These features depend, in their turn, on the valence state (the type of hybridization).

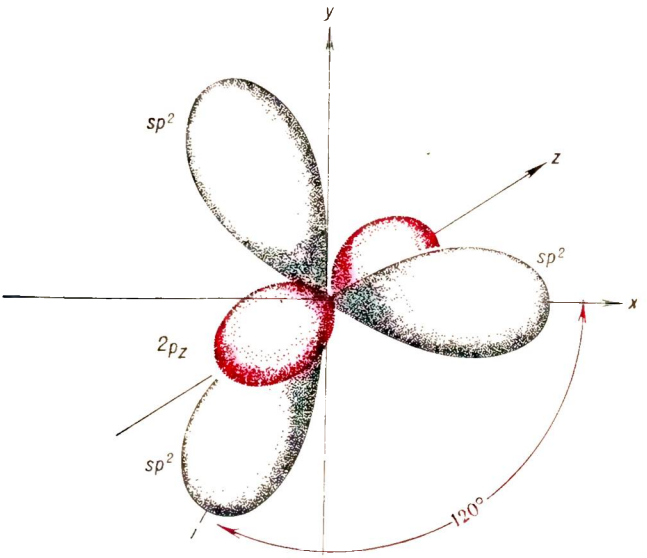
In a state of $sp^3$-hybridization the carbon atom is linked to four substituents. If we imagine that the carbon atom is at the centre of a tetrahedron, then the substituents will be at the corners of this tetrahedron. An example is the methane molecule, whose geometry is as follows:



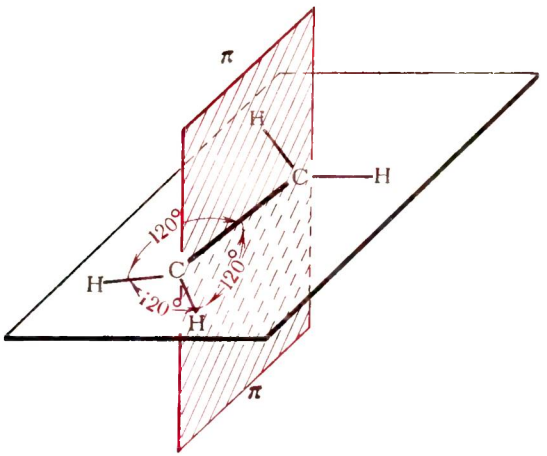

The tetrahedral model advanced in 1874 by van't Hoff as a hypothesis is supported now by experimental data. The X-ray diffraction, electron diffraction, and other methods are used to determine bond angles and interatomic distances (bond lengths). If all the four substituents are identical ($CH_4$, $CCl_4$), the model is a regular tetrahedron with bond angles of 109°28′. If the substituents attached to the carbon atom are different, the bond angles may depart by several degrees from the tetrahedral angles; the bond lengths will also be different — the tetrahedron will become irregular. An example of such a distorted tetrahedron is the molecule of monochlorodimethyl ether:



In a state of $sp^2$-hybridization the carbon atom is united to three substituents, all the four atoms lying in one plane and the bond angles being equal to 120°.

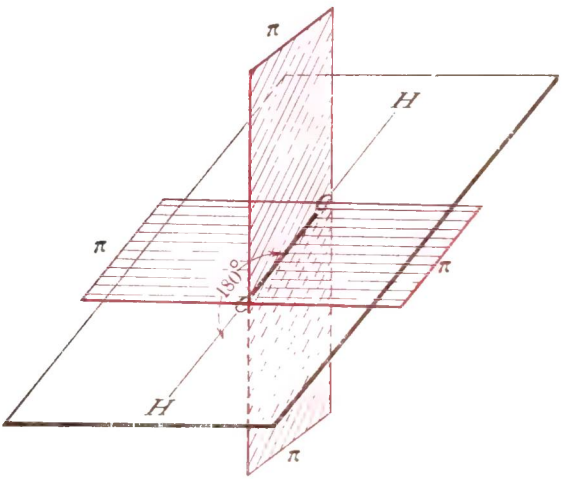



Between two adjacent carbon atoms being in a state of $sp^2$-hybridization there is formed not only an ordinary σ-bond but also a second bond of a special type. This latter type, called the π-bond, is formed by the overlap of *p*-orbitals which remained unhybridized:



The maximum overlap can be achieved with the parallel disposition of *p*-orbitals: it is this disposition which is energetically the most favourable. For this parallel arrangement to be disturbed, some energy must be consumed to break the π-bonds. Therefore, no free rotation about the carbon-carbon double bond is present; the important consequences arising from the lack of free rotation about the double bond will be considered at a later time.

The carbon atom in a state of *sp*-hybridization is linked to two substituents; all the four atoms of a system with a triple bond lie on a single straight line, and the bond angle is 180°.




## 1.3. BOND CHARACTERISTICS

Physical methods of investigation have made it possible to determine, to a high degree of accuracy, the geometric parameters of molecules, such as interatomic distances (bond lengths) and bond angles. These parameters are primarily dependent on the nature of atoms and the type of bond joining them, but a certain (sometimes, very strong) effect is also exerted by the nearest environment — the adjacent atoms and bonds. Here the bond angles vary rather readily within a few degrees, but for the normal interatomic distances to be changed a considerable energy is required.

Table 1.1 gives the characteristics of different types of bonds*. Apart from the geometrical parameters — bond lengths and valence angles (or bond angles), Table 1.1 lists other characteristics too: bond energies, bond polarities and polarizabilities. Though formally the last-mentioned bond characteristics have no relation to the subject matter of stereochemistry, they are in fact rather important in any theoretical treatment of the properties of molecules.

Precise determinations of bond lengths, valence angles and other parameters enable a *more detailed characterization* of individual compounds. The differences between compounds are associated, in a certain manner, with the constitution and reflect the mutual influence of atoms, which is taken to mean the manifestation of steric and electronic effects.

Pauling has shown that each covalently bonded atom occupies a certain definite volume, which does not depend, at a first approximation, on the nature of the second partner. Therefore, the lengths of covalent bonds may be regarded as the sums of the **covalent radii** of bonded atoms. The values of covalent radii are presented in Table 1.2.

## 1.4. MOLECULAR MODELS

Drawings cannot provide a sufficiently spectacular representation of the spatial structure of molecules; it is very useful to have "molecular models" to help us understand the three-dimensional structure of molecules more clearly.

At present, use is most often made of two types of models. The simplest type is known as **ball-and-stick models,** in which atoms are represented by balls joined by sticks built in at the corresponding angles; sticks are used to represent bonds (Fig. 1.1). In another version, holes are drilled in spheres (or polyhedrons), and rods of different lengths are placed into these holes: it is thus possible to model more exactly different bond lengths (interatomic distances) (Fig. 1.2). Such models give information about the spatial relationships of atoms in a molecule: when rods are made to correct scale, they also precisely represent the distances between the centres of the atoms.

However, the habit to visualize molecules in the form of ball-and-stick models creates a false impression of the atoms being at considerable distances from each other (see Fig. 1.2). This is not the case in reality: the atoms in the molecule are packed tightly, the chemically bonded atoms

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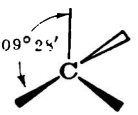
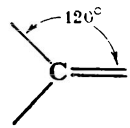
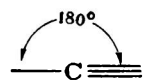
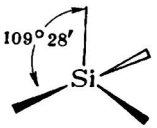
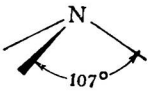
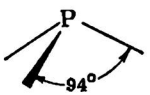
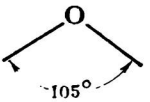
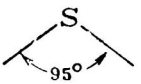
* In this book, energy is expressed in kilojoules per mole (kJ/mole) in accordance with the International System of Units (SI). To convert the numerical values expressed in kJ/mole to the usual values still more frequently encountered in the literature (kcal/mole), they must be divided by 4.19.

TABLE 1.1. THE CHARACTERISTICS OF COVALENT BONDS

| Type of bond | Bond length, Å | Energy | | Dipole moment *, D | Polarizability, cm³ |
|---|---|---|---|---|---|
| | | kJ/mole | kcal/mole | | |
| The carbon atom is in a state of $sp^3$-hybridization (the tetrahedral structure)  | | | | | |
| C—As | 1.98 | — | — | — | — |
| C—Br | 1.94 | 277 | 66 | 1.42 | 9.4 |
| C—C | 1.54 | 348 | 83 | 0 | 1.3 |
| C—Cl | 1.76 | 331 | 79 | 1.47 | 6.5 |
| C—F | 1.40 | 473 | 116 | 1.39 | 1.6 |
| C—H | 1.10 | 373 | 99 | 0.4 | 1.7 |
| C—Hg | 2.10 | 218 | 52 | — | 7.2 |
| C—I | 2.13 | 239 | 57 | 1.25 | 14.6 |
| C—N | 1.47 | 293 | 70 | 0.45 | 1.6 |
| C—O | 1.43 | 344 | 82 | 0.7 | 1.5 |
| C—P | 1.87 | 264 | 63 | — | 3.6 |
| C—S | 1.81 | 260 | 62 | 0.8 | 4.6 |
| C—Si | 1.87 | 243 | 58 | 1.2 | 2.5 |
| The carbon atom is in a state of $sp^2$-hybridization (the planar structure)  | | | | | |
| C=C | 1.34 | 620 | 148 | 0 | 4.2 |
| C=N | 1.27 | 616 | 147 | 1.4 | 3.8 |
| C=O | 1.21 | 708 | 169 | 2.4 | 3.3 |
| C=S | 1.6 | 432 | 103 | 2.0 | 11.9 |
| The carbon atom is in a state of $sp$-hybridization (the linear structure)  | | | | | |
| C≡C | 1.20 | 814 | 194 | 0 | 5.9 |
| C≡N | 1.15 | 882 | 210 | 3.1 | 4.8 |

| Type of bond | Bond length, Å | Energy | | Dipole moment*, D | Polarizability, cm³ |
|---|---|---|---|---|---|
| | | kJ/mole | kcal/mole | | |
| **The silicon atom (the tetrahedral structure)** | | | |   | |
| Si—Br | 2.3 | 289 | 69 | — | 10.1 |
| Si—Cl | 2.1 | 361 | 86 | — | 7.1 |
| Si—F | 1.8 | 542 | 129 | — | 1.7 |
| Si—H | 1.5 | 318 | 76 | 1.0 | 3.2 |
| Si—I | 2.5 | 214 | 51 | — | — |
| Si—N | 2.1 | — | — | 1.55 | 2.2 |
| Si—O | 1.8 | 369 | 88 | — | 1.8 |
| **The nitrogen atom (the pyramidal structure)** | | | |   | |
| N—H | 1.01 | 390 | 93 | 1.31 | 1.8 |
| N—N | 1.48 | 159 | 38 | 0 | 2.0 |
| N=N | 1.26 | 419 | 100 | 0 | 4.1 |
| N—O | 1.37 | 201 | 48 | — | 2.4 |
| N=O | 1.12 | 377 | 90 | — | 4.0 |
| **The phosphorus atom (the pyramidal structure)** | | | |   | |
| P—Cl | 2.1 | 319 | 76 | 0.81 | 8.9 |
| P—H | 1.4 | 319 | 76 | — | 4.0 |
| P—N | 1.7 | 216 | 50 | — | — |
| P—O | 1.6 | 353 | 84 | — | 3.1 |

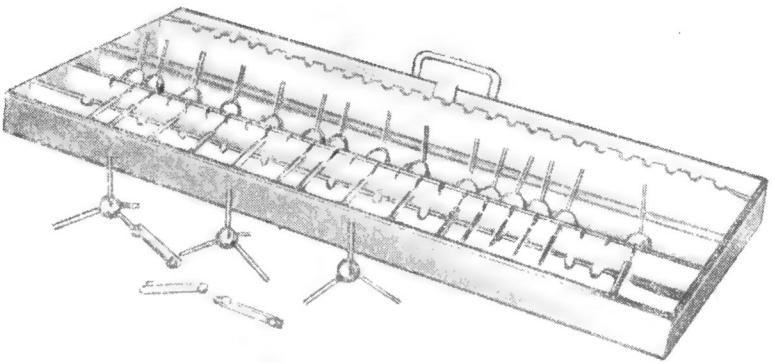
| Type of bond | Bond length, Å | Energy | | Dipole moment*, D | Polarizability, cm³ |
|---|---|---|---|---|---|
| | | kJ/mole | kcal/mole | | |
| **The oxygen atom (the non-linear structure)** | | | |  | |
| O—H | 0.96 | 466 | 111 | 1.51 | 1.7 |
| **The sulphur atom (the non-linear structure)** | | | |  | |
| S—H | 1.3 | 348 | 83 | 0.7 | 4.8 |
| S—N | 1.7 | — | — | — | — |
| S—O | 1.7 | — | — | — | 4.9 |
| S=O | 1.5 | — | — | — | −0.20 |

* The dipole moments are given on the assumption that the dipole moment of the C—H bond is equal to 0.4D with a positive charge on the hydrogen atom; other values for the dipole moments of the bonds may also be encountered in the literature, which are calculated on the basis of the reversed polarity of the C—H bond ($C^{\delta+}$—$H^{\delta-}$): they differ by 0.8D.

TABLE 1.2. THE COVALENT RADII OF ATOMS

| Atom and its valence state | Covalent radius, Å | Atom and its valence state | Covalent radius, Å |
|---|---|---|---|
| As | 1.21 | I | 1.35 |
| Br | 1.14 | N— | 0.70 |
| C— | 0.77 | N= | 0.60 |
| C= | 0.67 | N≡ | 0.55 |
| C≡ | 0.60 | Ni | 1.19 |
| Cu(II) | 1.35 | O— | 0.66 |
| Co(III) | 1.20 | O= | 0.55 |
| F | 0.64 | P | 1.11 |
| H | 0.30 | S— | 1.04 |
| Hg | 1.48 | S= | 0.94 |
| | | Si | 1.15 |

Figure 1.1.



*The simplest types of ball-and-stick models.*

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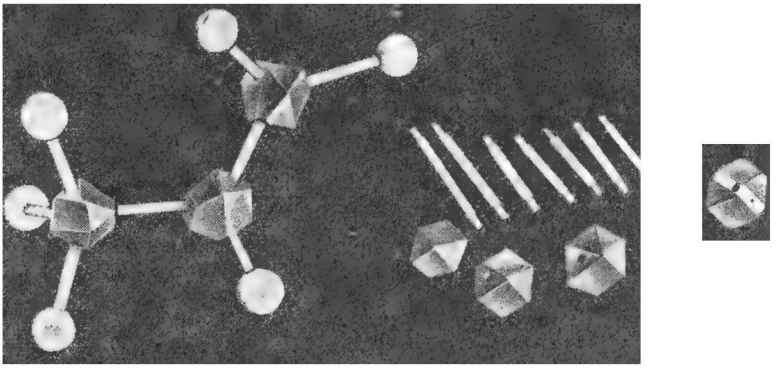
Figure 1.2.



***Ball-and-stick models with different bond lengths.***

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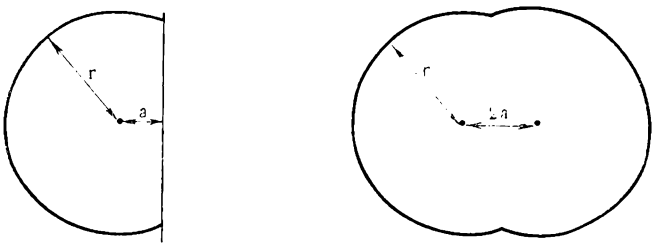
Figure 1.3.




A B

*Construction of space-filling models. The model of the hydrogen atom (A) and of the hydrogen molecule (B).*
*r — van der Waals radius (1.2 Å) ; a — covalent radius (0.3 Å) ; 2a — the H—H bond length (0.6 Å).*

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are directly contiguous to each other, and the distances between the nuclei are not just open space; they contain the orbitals in which the electrons are found.

A correct idea of the filling of the intramolecular space is provided by **space-filling** or **scale models** (Stuart-Briegleb models). The atoms in these models are represented by spheres sawed off at right angles, the radii of which correspond to the van der Waals radii which limit the sphere where there is no space for any other atom not bonded chemically with a given atom. For example, the van der Waals radius of the hydrogen atom is 1.2 Å. If we attempt to construct, with the aid of such spheres, a model for the hydrogen molecule, it will turn out that the centres of the atoms are at a distance of 1.2 + 1.2 = 2.4 Å, which by no means corresponds to the actual distance in the hydrogen molecule (which is only 0.6 Å). In order to obtain the correct distance between the atomic centres (the correct bond length), one must slice off part of the spheres (just as we cut off a slice of lemon or apple) and join the atoms together by their flat surfaces. The construction of space-filling models for the hydrogen atom and molecule is shown in Fig. 1.3. In this model, the bond length (0.6 Å) and the atomic dimensions are to scale.

The atom of a divalent element, say, oxygen, is represented as a sphere with two slices made at angles of 105° (the bond angle of oxygen). Using the scale models of the oxygen and hydrogen atoms, one can construct the space-filling model of water (Fig. 1.4).

The carbon atom in a state of $sp^3$-hybridization should be constructed in the form of a sphere with a radius of 1.8 Å (the van der Waals radius of the carbon atom) and four portions must be sliced off from it symmetrically so that the distance from the centre of the sphere to the slice

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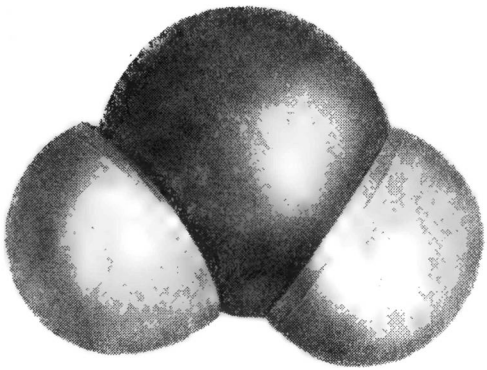
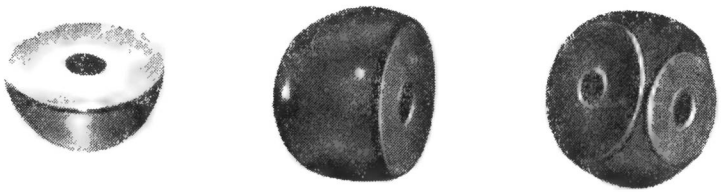
Figure 1.4.



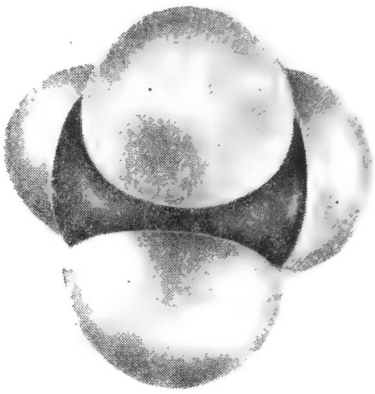
*The space-filling model of the water molecule.*

Figure 1.5.




*Scale models of hydrogen (a), oxygen (b) and carbon (c) atoms.*

Figure 1.6.



*The space-filling model of the methane molecule.*

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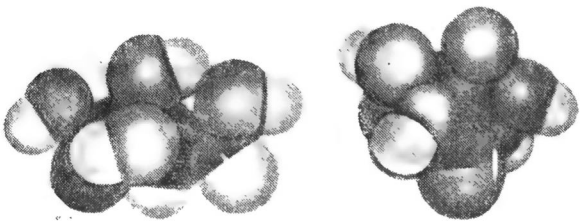
Figure 1.7.



a b

*Space-filling models of (−)-tartaric acid (a) and mesotartaric acid (b).*

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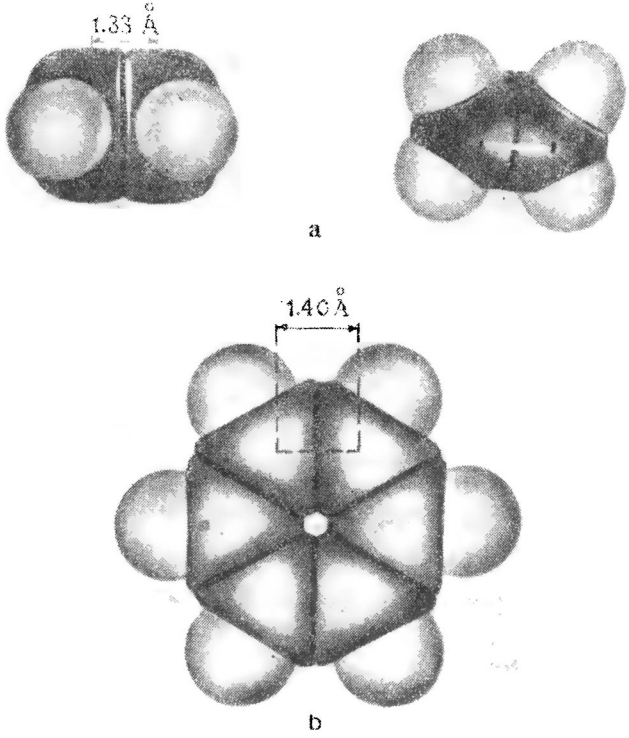
Figure 1.8.

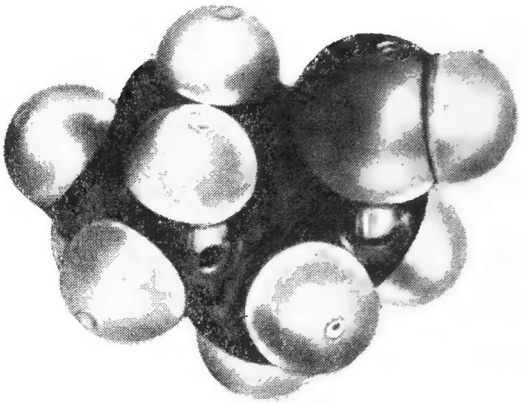



*Scale models of the molecules of ethylene (a—two different projections) and benzene (b).*

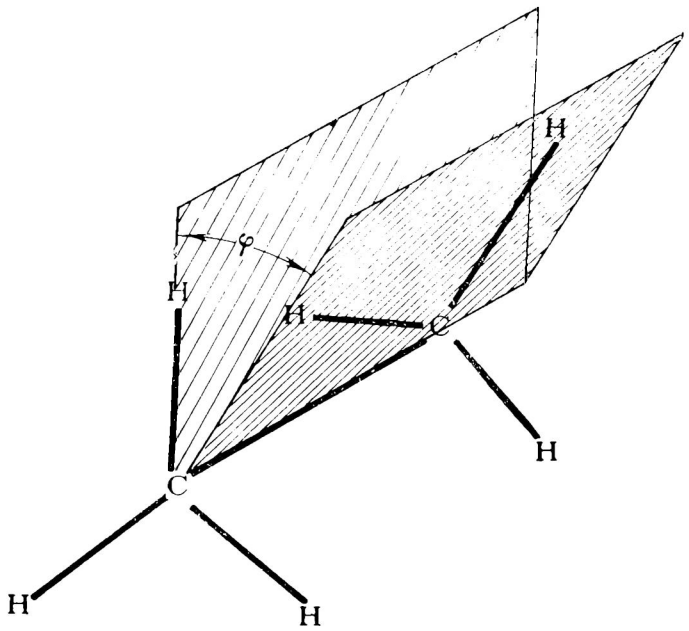
surface is equal to the covalent radius, 0.77 Å (Figs. 1.5 and 1.6). To construct the models of ethylenic, acetylenic, allenic and aromatic compounds, other models of the carbon atom are required. Similarly, special models are used to represent the oxygen atom linked by a double bond, the nitrogen atom linked by a double or a triple bond, etc. Using sets of the corresponding atoms, it is possible to build up models of complex organic compounds (Figs. 1.7 and 1.8).

Molecular models are usually made of wood or plastics, and the atoms are connected with studs or snap fasteners. There have appeared very original hollow plastic models of atoms which are directly fixed to each other (Fig. 1.9).

Figure 1.9.



*The space-filling model of the cyclohexanol molecule.*



The development of the printing art has made it possible to approach the solution of the problem of producing stereo (three-dimensional) illustrations. Three methods are employed at present. The first is as follows: each stereo illustration consists of a pair of drawings which, at first glance, appear to be identical; actually they are slightly different. When viewed in such a way that the left eye focuses on the left drawing and the right eye focuses on the right drawing (using a stereo viewer), your mind brings them together and creates a three-dimensional image (1). In the second method, which is called the anaglyphic method, the stereo effect is produced because each eye receives a specific image filtered through coloured spectacles from the two-colour anaglyphic drawing. Both coloured drawings fuse, creating a three-dimensional black-and-white image.

The third method, which is technically more involved, is based on the use of a screen — a plastic film with a large number of tiny lenses which cover a colour photographic image taken with the aid of a special multi-objective camera. When such a photograph is viewed, not only a three-dimensional coloured image is produced but it is possible, by changing the position, to view the three-dimensional object from the various positions.

Anaglyphic drawings are used rather widely. The full colour Hograph print technique using screens is more expensive and has not yet find wide application. One of the issues of the American journal "Biochemistry" has published an insert — the colour Hograph stereoscopic picture of the model of the molecule (2).

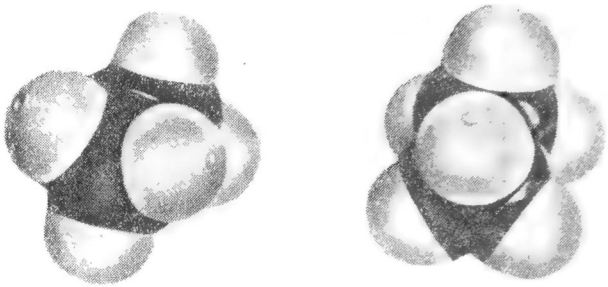
The latest method of recording a three-dimensional object on a photographic plate using the laser ray—holography—is still in the initial stage of development.

## 1.5. CONFORMATIONS (ROTATIONAL ISOMERISM)

The change from the simplest organic compound, methane, to its nearest homologue, ethane, raises new problems of spatial structure before the researcher, the solution of which requires a knowledge of parameters other than those considered in Sec. 1.3. As a matter of fact, one can visualize a large variety of geometrical forms of ethane without changing the valence angles and bond lengths. These forms differ from one another in mutual rotation of the carbon tetrahedra about the carbon-carbon single bonds uniting them.

The firmly established experimental fact—the absence of actually existing isomers of ethane and other similar compounds, which differ by the dihedral angle $\varphi$, made the chemists to assume, for a long time, that in this and other cases the internal rotation about a single bond

Figure 1.10.



*Scale models of two conformations of ethane.*

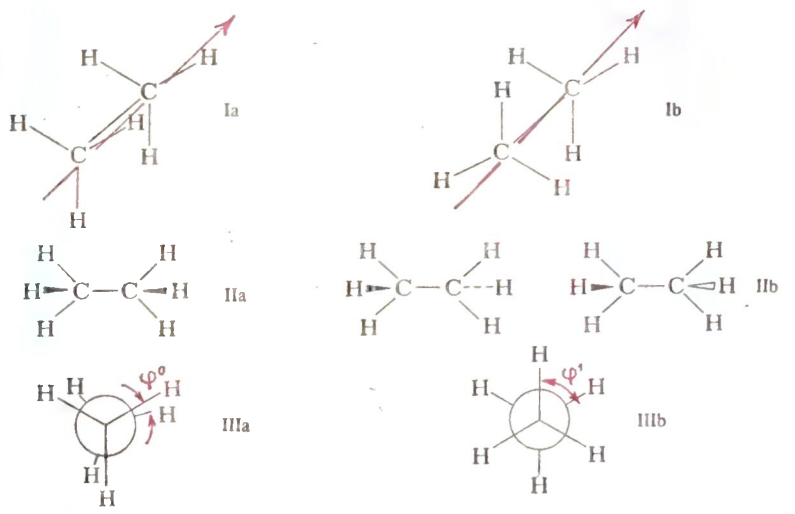
was completely free. Several decades ago the study of spectra, dipole moments and other physical properties led to the revision of this conception.

In 1936, Pitzer showed, for the first time, that for the calculated entropy of ethane to be consistent with the observed value it was necessary to assume the existence of a barrier (about 13 kJ/mole or 3 kcal/mole) hindering the rotation about the carbon-carbon single bond. This work served as the starting point for the development of conformational concepts, though actually the idea of the existence of various spatial forms of molecules with single bonds was advanced as early as 1890 by Sachse for cyclohexane.

This led Pitzer to suggest that there was restricted rotation about the single bond, which means that this rotation gives rise to **rotational isomers (conformers)**. The energies of various conformers are different and therefore the probability of finding the molecule in a given state is also unequal. The molecules of organic compounds tend to assume, through the rotation about the single bond, the most stable (under the given conditions), energetically favourable form. The energy barrier that separates the different rotational isomers is usually not great. Therefore, under ordinary conditions, it is impossible, as a rule, to fix or "freeze" molecules in any one strictly definite conformation: there usually exist several readily interconvertible rotational forms. Using another terminology, one speaks of the equilibration between the various conformations of molecules.

The study of the conformations of organic molecules has developed for the last several decades into a vast and important area of stereochemistry — **conformational analysis.** The development of conformational conceptions was the most significant step forward in the field of stereochemistry since the time of van't Hoff. Since conformations will be the subject matter throughout the book, it is especially important at the very outset to master methods of graphical representation of conformations and the corresponding nomenclature.

We shall begin with the ethane molecule. The existence of two extreme conformations of sharply differing energies can be predicted for ethane (Fig. 1.10). They are shown below in the form of perspective projections (Ia, Ib), side-view projections (IIa, IIb) and Newman formulas (IIIa, IIIb).

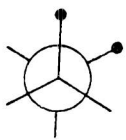
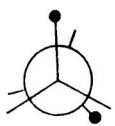


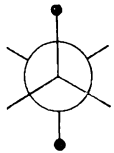
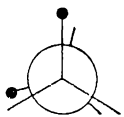
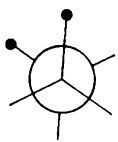

Fully eclipsed conformation, $\varphi = 0$ Staggered (skew) conformation, $\varphi = 1$

In the perspective (sawhorse) projection the carbon-carbon single bond is oriented diagonally backward: the left-hand carbon atom projects forward toward the viewer and the right-hand carbon atom projects away from the viewer.

In a side-view projection, four hydrogen atoms lie in the plane of the drawing; the carbon atoms, in fact, go somewhat beyond this plane, but usually, in a simplified approach, they are also considered to lie in the plane of the drawing. The heavy triangular (wedge-like) bond indicates a bond directed toward the viewer and the unfilled wedge bond (or a dashed-line bond) is a bond behind the plane of the paper.

TABLE 1.3. NAMES OF CONFORMATIONS

| Newman Projection | Symbol | Name | | | |
|---|---|---|---|---|---|
| | | English | German | Russian | According to Klyne and Prelog (5) |
| | $\varphi^0$ | Fully eclipsed, cisoid, cis | Ekliptisch, verdeckt, planar-syn, Atom-Atom | Цисоидная, эклиптическая, полностью заслоненная, затененная, *цис-*, *син-*, *сип*-планарная | ±synperiplanar |
|  | $\varphi^1$ | Gauche, skew | Windschief, syn, schief-syn | Скошенная, шахматная, *гош-* | +synclinal |
|  | $\varphi^2$ | Partially eclipsed | Teilweise verdeckt, schief-anti | Частично заслоненная, поворотная, 120° | +anticlinal |

| | | | | | |
|---|---|---|---|---|---|
|  | $\varphi^3$ | Fully staggered, anti, transoid, trans | Gestaffelt, planar-anti, auf Lücke, anti, trans, Atom-Lücke | Трансоидная, заторможенная, *анти-*, *транс-*, *анти*-планарная | ±antiperiplanar |
|  | $\varphi^4$ | See $\varphi^2$ | See $\varphi^2$ | See $\varphi^2$ | −anticlinal |
|  | $\varphi^5$ | See $\varphi^1$ | See $\varphi^1$ | See $\varphi^1$ | −synclinal |

In the Newman projections you view the molecule by looking down the carbon-carbon bond (in the direction indicated by the arrow in formulas Ia and Ib). The three lines that radiate from the centre of the circle at an angle of 120° represent the bonds of the carbon atom nearer to the eye and the carbon atom further from the eye is shown by a circle with three equally spaced radial extensions. Newman projections also specify conformations with the aid of the **angle of torsion** or **dihedral angle** $\varphi$: in a general case, it is measured between two senior substituents in a clockwise direction and is expressed in arbitrary units equal to 60°.

The conformation $\varphi^\circ$ shown on the left-hand side (IIIa) is called the **eclipsed conformation** in which the hydrogens on the rear carbon are directly behind those on the front carbon (although in the drawing they are offset a little for clarity). Another term for this conformation is the cisoid or *cis* conformation; in this case $\varphi = 0, 2, 4$.

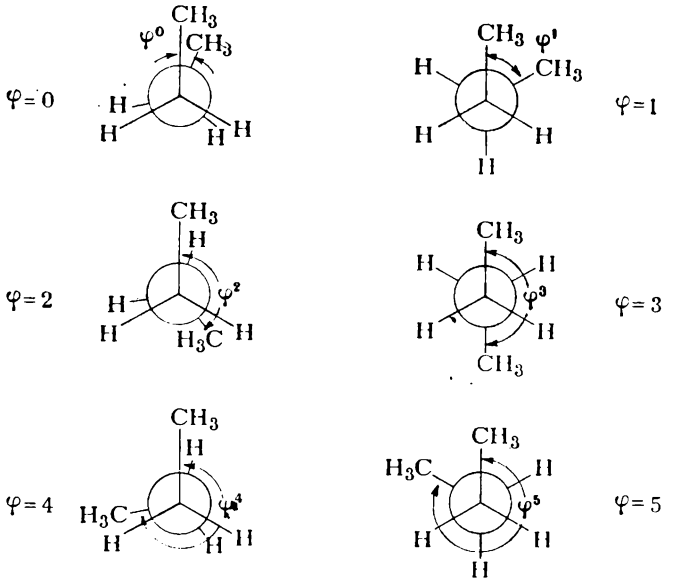
The conformation $\varphi^1$ shown on the right-hand side (IIIb) is called the **staggered conformation** in which the hydrogen atoms on the two carbon atoms are farthest apart; free rotation about the carbon-carbon single bond is hindered in this position, i.e., the molecule exists predominantly in this conformation. Rotational isomers of this type are also known as the *trans* conformations ($\varphi = 1, 3, 5$).

As a general rule, the eclipsed conformations cannot be adopted by molecules without distortion of the normal angles and bond lengths; such conformations have an increased internal energy and are therefore unfavourable. Molecules practically always exist only in the staggered conformations.

As the molecule becomes more and more complex, the number of possible conformations differing significantly in energy content increases. For example, *n*-butane may be represented by six conformations which differ in the relative disposition of the $CH_3$ (methyl) groups, i.e., in the rotation about the central carbon-carbon single bond. The conformations of *n*-butane are shown below as Newman projections. The eclipsed conformations on the left (*cis* conformations) are energetically unfavourable: the *n*-butane molecules can practically exist only in the staggered conformations ($\varphi^1$, $\varphi^3$, $\varphi^5$). These conformations have specific names: $\varphi^3$ is the fully staggered conformation; $\varphi^1$ and $\varphi^5$ are called the skew forms (see the drawings on page 33).

Alternative names have been suggested for these conformations (see Table 1.3). Thus, the skew conformation is sometimes called the gauche conformation, and the fully staggered form is also known as the transoid, *trans* or *anti* conformation. The terms "trans" and "anti" are inconvenient since they are used in stereochemistry for other purposes. The various methods of designating conformations are described in detail in the literature (3).

In the example given above, rotational isomerism has been regarded as a consequence of rotation about one single bond.

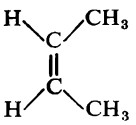



But even in the case of *n*-pentane we must take into account the rotation about two "internal" carbon-carbon single bonds. With increasing complexity of molecules the number of possible conformations increases and graphical representation becomes complicated. It should also be kept in mind that not only the rotation about single bonds but also other intramolecular movements of atoms may give rise to the various geometrical forms of molecules and conformations. Therefore, the widely used definition of conformations as "the non-identical arrangements of the atoms obtainable by rotation about one or more single bonds" is not quite correct (4). This definition is criticized, for example, by Robinson (5).

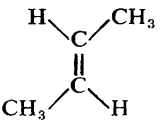
In the most general form, conformations may be defined as the various non-identical spatial forms of a molecule having a definite structure and a definite configuration (6). Conformations (conformers) are stereoisomeric structures which are in dynamic (mobile) equilibrium and are capable of interconverting by way of inversion or buckling of the bonds, and through rotation about single bonds. In some cases, the barrier to such interconversions becomes sufficiently high for the stereoisomeric forms to be separated (an example is provided by optically active biphenyls). In such cases, one speaks of the actually existing **isomers** rather than of conformers. It is easy to see that there is no sharply distinct boundary line between conformers (conformational isomers) and actually existing, stable stereoisomers.

## 1.6. GEOMETRICAL ISOMERISM

An important consequence of the rigidity of the double bond (the lack of free rotation about it) is the existence of **geometrical isomers.** The term **geometrical isomerism** is applied to isomerism that depends upon the arrangement of substituents on a double bond or on a cyclic structure. The most widespread isomers of this type are **cis-trans isomers** of compounds of the ethylene series, which contain non-equivalent substituents at unsaturated atoms. As the simplest example may be cited the isomers of 2-butene:



*cis*-2-Butene



*trans*-2-Butene

| | | |
|---|---|---|
| Melting point | −138.9°C | −105.6°C |
| Boiling point | 3.72°C | 1.0°C |
| Heat of hydrogenation | −120 kJ/mole (−28.6 kcal/mole) | −116 kJ/mole (−27.6 kcal/mole) |
| Heat of combustion | 2720 kJ/mole (647.8 kcal/mole) | 2716 kJ/mole (646.8 kcal/mole) |
| $d_4^t$ | 0.724 (at −78.5°C) | 0.604 (at 20°C) |
| $n_D^{20}$ | 1.3946 | 1.3862 |

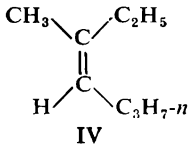
Geometrical isomers have an identical chemical constitution (the same order of chemical bond between atoms) and differ in the spatial arrangement of atoms (in **configuration).** It is this difference in the configuration of atoms that is responsible for different physical (and chemical) properties; in fact, geometrical isomers are different compounds. In the case of 2-butene these differences are not great, but in other cases they may be more significant.

Geometrical isomers can be isolated in a pure form; they exist as individual stable compounds. For their interconversion to take place there is usually required an energy of the order of 120-170 kJ/mole (30-40 kcal/mole). Such an energy can be provided by heating, ultraviolet irradiation, and by other types of radiation.

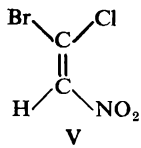
Comparing geometrical isomers with conformers, we may say that geometrical isomers are, as it were, "fixed" or "frosen" conformers which have become stable owing to the high energy barrier to rotation about the double bond. Not infrequently, geometrical isomers are now regarded as belonging to a certain type of diastereomers (see page 52).

Representation of the configurations of geometrical isomers involves no difficulties: unsaturated carbon atoms and four of their nearest sub-

stituents lie in the plane of the paper, and the plane of the π-bond must be visualized as being perpendicular to the plane of the drawing. In the simplest cases, the nomenclature is not difficult either: geometrical isomers in which identical atoms or groups are on the same side of the plane of the π-bond are known as *cis*-compounds; in *trans*-isomers the identical substituents are on opposite sides of the molecule. In more complicated cases, when all four substituents are different, the *cis-trans* notation cannot be understood without further explanations, as, for example, with molecules IV and V.



IV



V

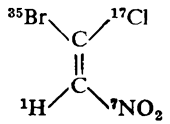
In such cases, use may be made of one of the two systems of nomenclature described below. One of these, the so-called ε,τ-system, which was suggested by Terentiev and co-workers in 1953 (8-9). The main principle of this system is as follows: the configuration is denoted by specifying the *cis* (ε) or *trans* (τ) arrangement of a pair of substituents of *highest priority* at the double bond. The priority of the substituents is determined in accordance with the conventional rules in the nomenclature of organic compounds. Therefore, substituents of highest priority in any compound, whose double bond is not at the end of the chain, will be portions of the main chain. Thus, formula IV represents 3-methyl-3-heptene. The highest-ranking unit in this structure is the main chain containing the $C_2H_5$ and $C_3H_7$ residues which are contiguous to the double bond. In formula IV, these residues are in the *cis*-position relative to each other, for which reason the structure IV is designated as 3-methyl-3ε-heptene. In structure V the bromine is higher-ranking than chlorine, hence the name: 2-chloro-2τ-bromine-1-nitroethylene.

Another system of nomenclature was proposed in 1968 (10) and has now been recommended by the IUPAC Commission on the Nomenclature of Organic Chemistry. (IUPAC meaning the International Union of Pure and Applied Chemistry). This system is based on the same principle as the ε,τ-nomenclature: it specifies the *cis* (*Z*) or *trans* (*E*) position of substituents of higher priority about the double bond. The only difference is that in the *Z,E*-system the priority is determined by the **sequence rule** on the basis of calculations of the atomic numbers (11).

In the *Z,E*-system, according to the sequence rule, the substituents are arranged in order of *decreasing atomic number* of the atoms by which they are bound to the asymmetric carbon atom, priority being given to the group in which the first atom has the highest atomic number. If the atoms linked directly to unsaturated carbon atoms have the same

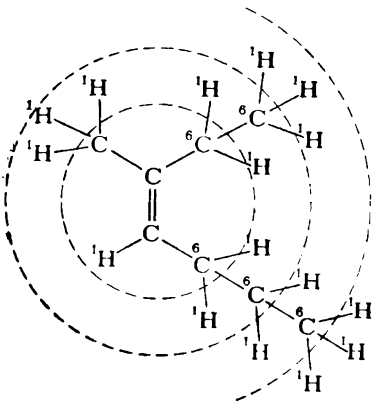
atomic number (as, for example, the carbon atoms in the upper part of formula IV), then the relative priority is determined by a similar comparison of the atomic numbers of the *next* atoms in the groups (i.e., the atoms joined to the atom linked to the asymmetric carbon atom; the atoms of the second sets). If the second atoms afford no choice, one goes to the third set, etc. Thus one works *outwards* from the asymmetric carbon atom until a selection can be made for the priority sequence of the groups.

Let us begin with formula V, where the problem is solved by the first atoms. Their atomic numbers are indicated:




The substituents of higher priority in each pair (bromine in the upper part and nitrogen in the lower part) are in the *trans*-position, and the configuration is assigned the stereochemical descriptor *E* (from the German Entgegen meaning opposite).

For structure IV to be described configurationally, it is necessary to look for a difference in the next second sets.

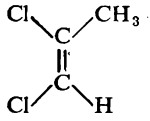


The groups $CH_3$, $C_2H_5$, and $C_3H_7$ do not differ from one another with respect to the first atoms. As regards the second atoms, in the $CH_3$ group the sum of the atomic numbers is equal to 3 (three hydrogen atoms), and the combined atomic number for each of the $C_2H_5$ and $C_3H_7$ groups is 8. It means that the $CH_3$ group is dropped since it is of lower priority than the other two groups. Thus, precedence is given to the two groups of higher priority, $C_2H_5$ and $C_3H_7$; they are in the *cis*-

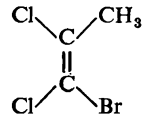
position and the stereochemical descriptor *Z* is used to designate the configuration (from the German Zusammen meaning together).

Had we to determine the priority sequence of the $C_2H_5$ and $C_3H_7$ groups, we would have to consider the third atoms: the combined atomic numbers in the third set would be respectively equal to 3 and 8, i.e., precedence would be given to the $C_3H_7$ group. In more complicated cases of priority determination based on the sequence rule, some additional conditions are to be taken into consideration: the atom attached by a multiple bond is counted twice (double bond) or three times (triple bond); if two atoms are isotopes, then the one with the higher mass number precedes the lower (e.g. deuterium is heavier than hydrogen).

It must be ascertained that the designations ε and *Z* are *not* synonyms of the *cis* notation just as τ and *E* do not always correspond to the *trans* notation. In the three systems of nomenclature, designations are selected in accordance with different rules, their combination being entirely dependent on the concrete specific features of the structure; for example,




*cis*-1,2-Dichloro-1-propene
1,2-dichloro-1τ-propene
*Z*-1,2-dichloro-1-propene



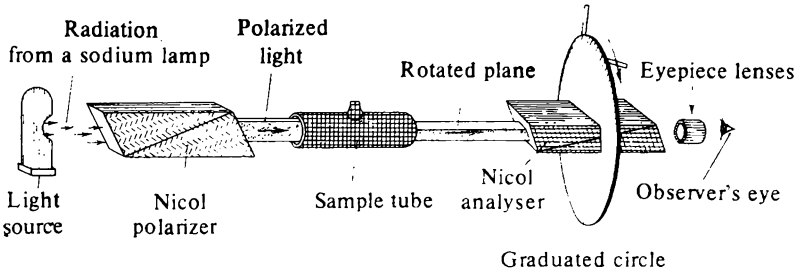

*cis*-1,2-Dichloro-1-bromo-1-propene
1,2-dichloro-1-bromo-1ε-propene
*E*-1,2-dichloro-1-bromo-1-propene

## 1.7. OPTICAL ISOMERISM (ENANTIOMERISM)

There are organic compounds that are capable of rotating the plane of polarized light. This phenomenon is called optical activity and the substances having this property are called **optically active** substances. Optical activity is observed and measured by means of an instrument known as a **polarimeter.** The schematic diagram of the polarimeter is shown in Fig. 1.11.

A ray of light from a light source is passed through a polarizer (a Nicol prism or polaroid film). The light transmitted by the polarizer is plane-polarized. If a second prism, called the analyser, is placed in the path of the polarized light, the light intensity passed through the analyser will depend on the relative orientation of the two prisms. The analyser can be turned so that the plane of polarization formed by it will be oriented in the same manner as the plane of polarization of the light emerging from the polarizer ("parallel Nicols"); in this case, the polarized light will pass through the system without being attenuated.

Figure 1.11.




*Schematic diagram of the polarimeter.*

Another limiting case arises when the polarization planes of both prisms are turned by 90° relative to each other ("crossed Nicols"), in this case no polarized light will be transmitted by the analyser. With any other relative orientation of the polarizer and analyser the light undergoes partial extinction.

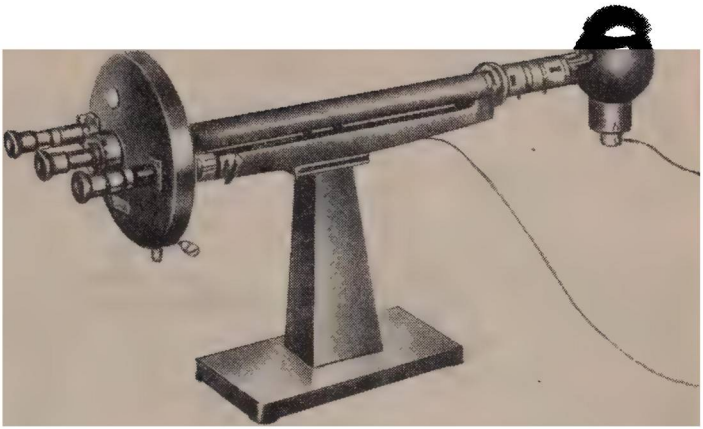
If a sample tube containing an optically active substance is placed (between the polarizer and the analyser) in a polarimeter with crossed Nicols, the light extinction by the analyser will be incomplete (due to the rotation of the plane of polarization). For complete extinction to be achieved, the analyser must be turned through a certain angle to the right (+) or to the left (—). This angle, $\alpha$, will then be the quantity sought, i.e., the angle to which the substance placed in the polarimeter rotates the plane of polarization.

Since a comparison of the light intensities of the contacting fields can be done visually with an incomparably higher precision than the determination of the position of complete extinction, a "half-shade" device is used in visual polarimeters, which makes it possible to reduce the measurement to the matching of the light intensities of two (or three) fields.

Modern polarimeters (Fig. 1.12) enable the angle of rotation to be measured with a very high precision (up to 0.001°). The visual instruments are more and more often replaced by photoelectric polarimeters (Fig. 1.13).

The ability to rotate the plane of polarization is exhibited by certain crystalline inorganic substances (e.g., quartz). The optical activity of organic compounds reveals itself not only in the crystalline but also in the liquid state, in solutions, and in vapour. This indicates that the optical activity of organic compounds is a property of the molecules themselves and is not associated with the crystal lattice.

Figure 1.12.



*Modern polarimeter.*

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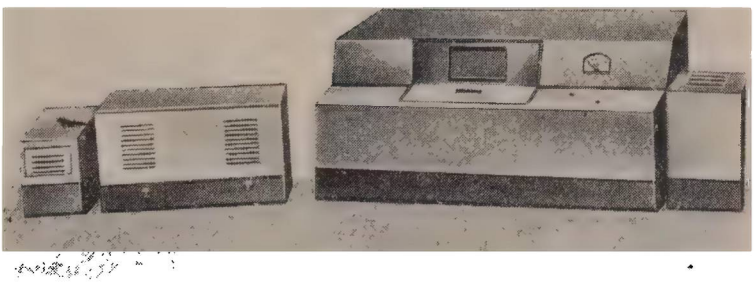
Figure 1.13.



*Modern photoelectric polarimeter.*

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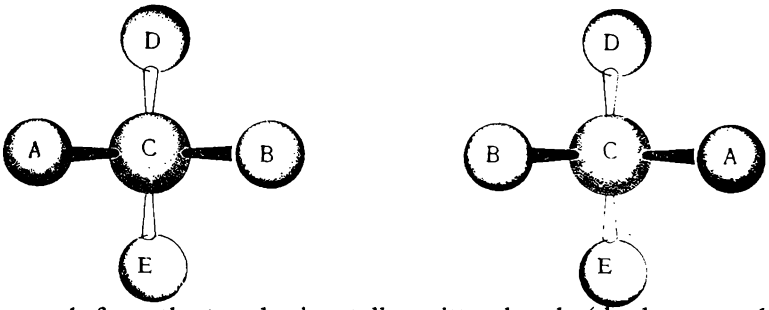
It has been found that optically active substances exist as pairs of **optical antipodes** or **enantiomers** *(enantiomorphs)*, which are isomers whose physical and chemical properties are identical under ordinary conditions (see page 62), except for the sign of rotation of the plane of polarization. If one of the antipodes has, say, a specific rotation of +20°, the specific rotation of the second antipode is −20°.

Contemplations about the factors responsible for optical isomerism led van't Hoff to postulate the idea of the tetrahedral carbon atom. Van't Hoff ascribed the optical activity of organic compounds to the lack of symmetry or **asymmetry** in their molecules. Symmetry is lost, in particular, when there is an asymmetric carbon atom in the molecule; a carbon atom that carries four different substituents is called an **asymmetric carbon atom.** Geometrical considerations suggest that two tetrahedral arrangements of substituents about the asymmetric carbon atom are possible.




Just as before, the two horizontally written bonds (the heavy wedges) project above, and the two vertically written bonds (the light wedges) project below the plane of the paper. In other words, the substituents A and B lie in front of the plane of the drawing and the substituents D and E lie behind this plane. The two spatial forms cannot be made to coincide by rotation. One of them is the mirror image of the other.

This type of spatial isomerism is known as optical isomerism, mirror-image isomerism, or enantiomerism (enantiomorphism). The two mirror-image forms constitute a pair of optical antipodes or enantiomorphs. They differ from each other by the sign of optical rotation, the amount of optical rotation being identical.

Finalizing what has been said above about the identity of all other properties of optical antipodes, it should be noted that this identity is lost under the influence of physical factors or chemical substances, which, in their turn, are asymmetric (circularly polarized light, optically active reagents).

The asymmetric carbon atom is the principal but not the only factor responsible for the optical activity of organic compounds. The atoms of other elements may also be asymmetric; examples are silicon, nitrogen,

phosphorus, arsenic, sulphur. Optical activity may even arise in the absence of an asymmetric atom, due to the asymmetry of the molecule as a whole **(molecular asymmetry)**. In complex compounds, asymmetry often appears in a three-dimensional octahedral structure.

## 1.8. POLARIMETRY AND SPECTROPOLARIMETRY

The measurement of optical rotation by means of a polarimeter is one of the oldest physico-chemical methods used in organic chemistry. The principles of such measurements have just been described.

The angle of rotation measured by the polarimeter depends on the length of the sample tube containing an optically active substance and, with solutions, on the sample concentration as well. This angle is then recalculated to the specific rotation. The **specific rotation,** $[\alpha]$, is defined as the rotation in degrees brought about by a liquid or a solution containing 1 gram of an optically active substance in 1 millilitre of solution, examined in a polarimeter tube having a length of 1 decimeter (10 cm). The specific rotation for a liquid is calculated by the formula:

$$[\alpha] = \frac{\alpha}{l \times d}$$

where $\alpha$ is the observed or actual rotation, i.e., the angle through which the plane of the light is rotated by the sample in a tube having a length of $l$ dm, the density of the substance being equal to $d$.

For solutions, the formula assumes the following form:

$$[\alpha] = \alpha \times \frac{100}{l \times c}$$

where $c$ is the number of grams of an optically active substance contained in 100 ml of solution (i.e., the bulk concentration).

In a practical determination of the specific rotation, a weighed amount of an optically active substance ($a$ grams) is dissolved in a measuring flask (a pycnometer) of $V$ ml capacity and the actual magnitude of optical rotation is determined. The formula given above adopts the following form after substitution of the quantities representing the weighed amount of substance and the volume of the solution:

$$[\alpha] = \frac{\alpha \times V}{l \times a}$$

Usually, to save the optically active substance, small measuring flasks are used (e.g., flasks of 3-10 ml capacity), and therefore the accuracy

of the concentration determined in this way will not be too high. More accurate results are obtained when the following formula is used for the calculations:

$$[\alpha] = \frac{\alpha \times A}{l \times a \times d}$$

where $A$ is the mass of the solution, $a$ is the weighed amount of an optically active substance, and $d$ is the density of the solution.

The specific rotation depends on the nature of the solvent, and varies with concentration for many substances. The numerical value of specific rotation is also affected by the wavelength at which the measurements are made (see below). When the measurements are reported, all of the above variables must be specified (the wavelength of the light and the temperature are often indicated by subscripts and superscripts, respectively, and the solvent and concentration are usually given in brackets). For example, for a 20 per cent solution of (+)-tartaric acid in water, the specific rotation measured at the wavelength of the sodium D-line at 20°C is equal to +11.98°. This is written as follows:

$$[\alpha]_D^{20} = +11.98^\circ \text{ (water, } c = 20)$$

The specific rotation is often replaced by **molecular rotation,** $[M]$, which is calculated by the formula:

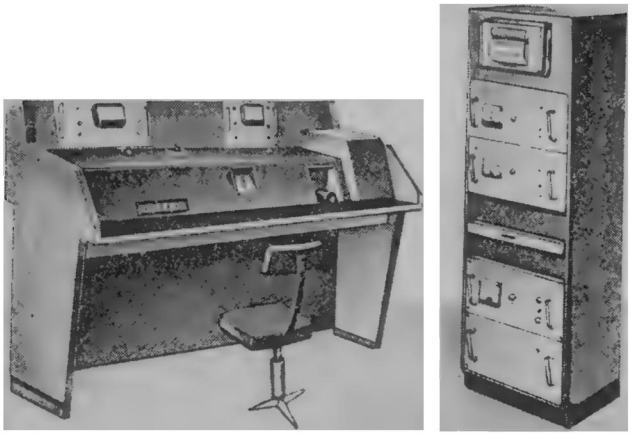
$$[M] = M \times \frac{[\alpha]}{100}$$

where $M$ is the molecular weight of the optically active substance.

As already mentioned, the numerical value of optical rotation depends on the wavelength of the light used in measurements. Traditionally, in polarimetric measurements, use is most frequently made of a sodium lamp as the light source (burners have been replaced by sodium-vapour lamps or filters), which radiates light of one wavelength, 589 nm (5893 Å). Many of the data on specific rotations reported in the literature refer to the green line of mercury (546 nm).

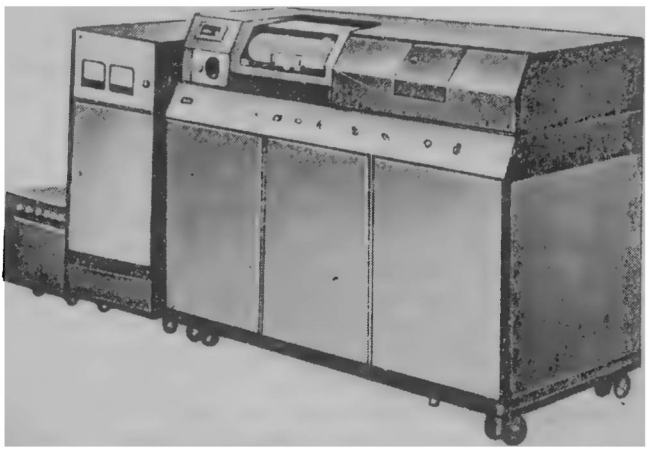
Wide use in the last few decades has been made of **spectropolarimetry**, in which the quantity measured is not the rotation at a single wavelength but the dependence of rotation on the wavelength over a wide spectral range. The instruments used are called **spectropolarimeters** (Figs. 1.14 and 1.15). The results obtained in spectropolarimetric measurements are expressed in the form of **optical rotatory dispersion curves** (ORD curves). Examples of such curves are given in Figs. 1.16 and 1.17. These figures clearly show that substances having identical or similar rotations at the D-line of sodium may have quite different ORD curves.

Figure 1.14.



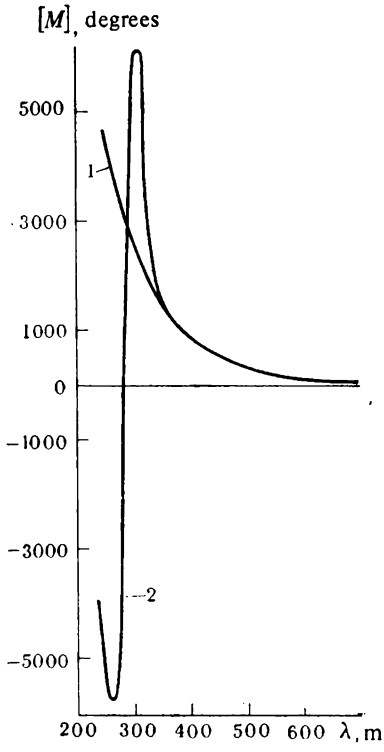
*Spectropolarimeter.*

Figure 1.15.



*Spectropolarimeter (Jasco J-20).*

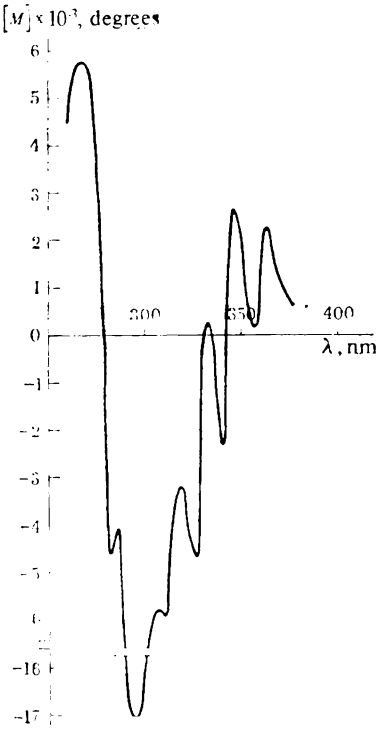
Figure 1.16.




*Types of optical rotatory dispersion (ORD) curves (1 mμ = 1 nm):*

*1 — plain curve; 2 — curve with a positive Cotton effect.*

Figure 1.17.

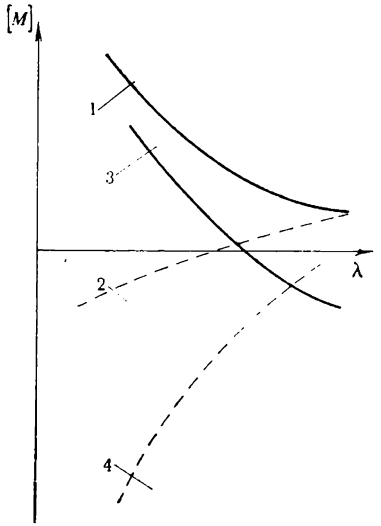



*The optical rotatory dispersion curve of (+)-3-methyl-1-indanone as an ORD curve with several Cotton effects.*

The character of ORD curves depends on the configuration and conformation of optically active substances, and also on the nature of the chromophores present and their position relative to the asymmetric centre. In many cases, ORD curves are significantly dependent on the solvent and temperature. All this makes spectropolarimetry an important physico-chemical method of investigation of organic compounds. Introducing an optically active radical into organic compounds that do not possess optical activity, it is possible to expand the range of substances accessible to investigation by the spectropolarimetric method.

For the character of ORD curves to be described without graphical representation, use is made of the following terminology. Curves that

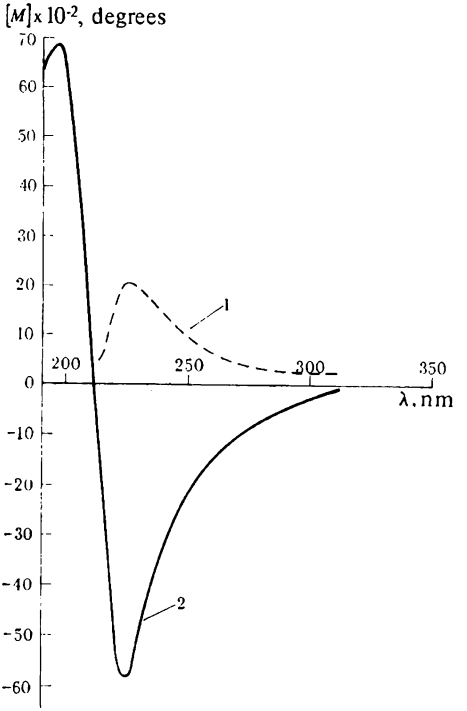
Figure 1.18.




*Plain ORD curves:*

*1 and 3 — plain positive curves; 2 and 4 — plain negative curves.*

Figure 1.19.

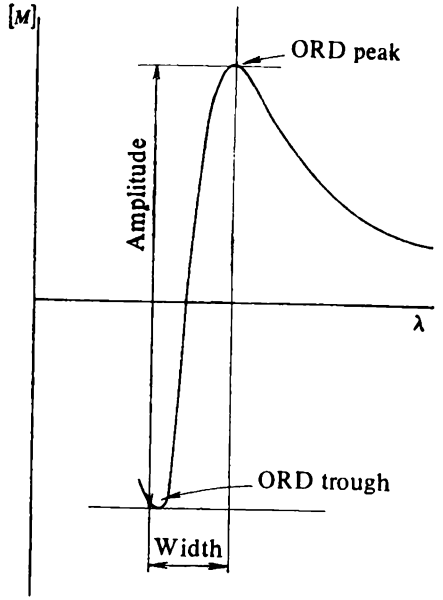



*The rotatory dispersion curves of (+)-2-hydroxyoctanoic acid (curve 1) with a positive Cotton effect and (+)-tartaric acid (curve 2) with a negative Cotton effect.*

ascend or descend monotonically are called **plain curves.** These curves may be positive or negative, depending on the slope of the curve to the abscissa (but not on the sign of rotation!), i.e., on whether they ascend or descend with decreasing wavelength (Fig. 1.18).

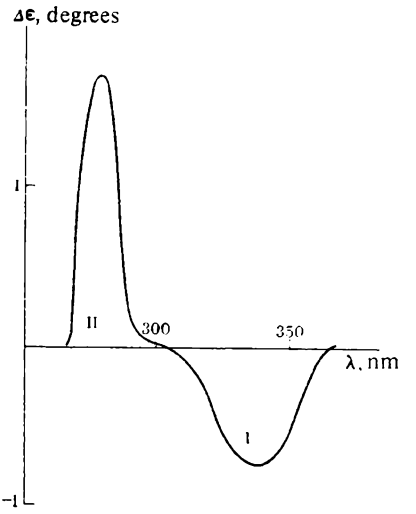
The positions of the extremal points on ORD curves with a Cotton effect, known as **Cotton effect curves,** are described by the terms **peaks** and **troughs** (the use of maxima and minima is not recommended because of the confusion that may arise since these terms are employed to describe ultraviolet spectra). A Cotton effect curve is labelled positive if

Figure 1.20.




*Terminology for describing ORD curves.*

Figure 1.21.




*The circular dichroism (CD) curve of (−)-N-dithiocarbethoxyaspartic acid:* I — *region of negative CD ;* II — *region of positive CD.*

---

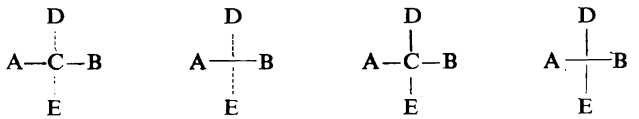
the peak is at a longer wavelength than the trough (Fig. 1.19, curve *1*); if the opposite is true, the ORD curve is negative (curve *2*). The sign of rotation is unimportant. Rotatory dispersion curves are also characterized by the amplitudes and widths of Cotton effects; the meaning of these terms is clear from Fig. 1.20.

Apart from the measurement of optical rotation over a wide spectral range, use is also made of another method that provides information on optically active absorption bands, this is the method of **circular dichroism** (CD). The instruments used for the purpose record curves characterizing the intensity of double circular absorption, i.e., the difference between the absorption coefficients for the left- and right-circularly polarized light. Circular dichroism curves provide, in general, the same information as rotatory dispersion curves, but the former are often more convenient for interpretation and theoretical calculations. An example of a circular dichroism curve is shown in Fig. 1.21.

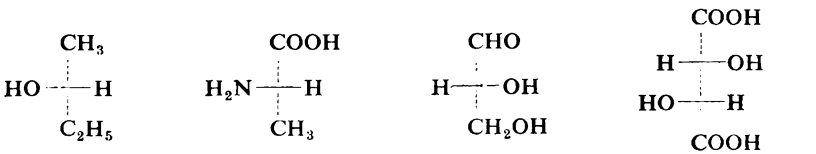
---

## 1.9. PROJECTION FORMULAS

For the asymmetric carbon atom to be represented in the plane, use is made of **Fischer projection formulas.** They are obtained by representing the picture shown on page 40 in the plane. The asymmetric atom is often omitted, and only the intersecting lines and the symbols for the substituents are shown. To remind of the three-dimensional arrangement of the substituents, it is very helpful to use a dotted vertical line in projection formulas (the north and south bonds extend behind the plane of the paper); unfortunately, this is seldom done. The convention of Fischer projection formulas is such that the east and west bonds of the asymmetric carbon are considered to protrude forward out of the plane of the paper and the north and south bonds to extend behind the plane of the paper. The different methods of writing projection formulas that correspond to the left-hand model on page 40 are given below:




Some examples of Fischer projection formulas written in the form used in this text are as follows:




(−)-2-Butanol (+)-Alanine (+)-Glyceraldehyde (+)-Tartaric acid

The last example presents a more complex optically active compound having two asymmetric carbon atoms in the molecule. Compounds with two or more asymmetric atoms have important specific features which will be described at a later time.

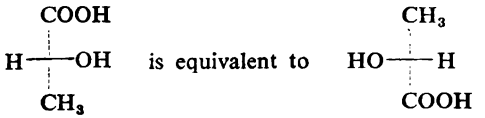
The names of the compounds given are preceded by their signs of rotation: this means, for example, that the levorotatory antipode of 2-butanol has the *spatial configuration* pictured exactly by the above formula, and its mirror image corresponds to the dextrorotatory 2-butanol. *Determination of the configuration* of optical antipodes is carried out experimentally, use being made of the methods which will be described in a special chapter.

In principle, each optical antipode and each model with one asymmetric carbon atom may be represented by twelve (!), outwardly dissim-

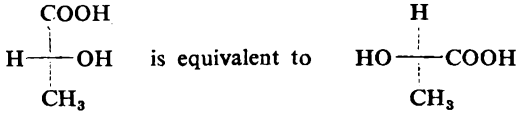
ilar projection formulas, depending on the disposition of the model in projection and the side from which it is viewed. To standardize projection formulas, certain rules must be observed in writing these formulas. Thus, the principal function (if it is at the end of the chain) is placed at the top of the projection formula, and the main (backbone) chain is arranged vertically.

In order to be able to compare "non-standard" projection formulas, it is necessary to know the following rules for the transformation of projection formulas.

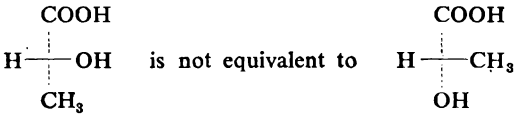
1. Projection formulas may be rotated 180° in the plane of the drawing without their stereochemical meaning being changed; the two projections shown refer to the same molecule:



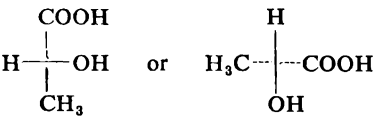

2. Two or any other *even number* of interchanges, or transpositions, of the substituents at one asymmetric atom do not alter the stereochemical meaning of the formula:



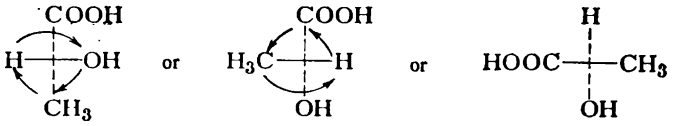

3. One such interchange or any other *odd number* of interchanges of the substituents at the asymmetric centre will lead to the formula of the optical antipode (enantiomer) of the original molecule:




4. The rotation in the plane of the drawing by 90° converts the molecule to its enantiomer provided that the arrangement of the substituents relative to the plane of the drawing is not simultaneously changed, i.e., if the horizontal bond is not assumed to project below the plane of the paper and the vertical bond above it. If we make use of a formula with a dotted line, the altered orientation of the dotted line will directly remind of this:

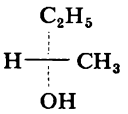


5. Apart from transpositions, projection formulas can be transformed by rotating a group of any three substituents in a clockwise or counterclockwise direction; the fourth substituent does not change its position (such a manipulation is equivalent to two interchanges):




6. Projection formulas may not be brought out of the plane of the drawing (i.e., one must not, for example, view them from the opposite side of the paper — the stereochemical meaning of the formula will be changed).

Let us consider, as an example, the projection formula



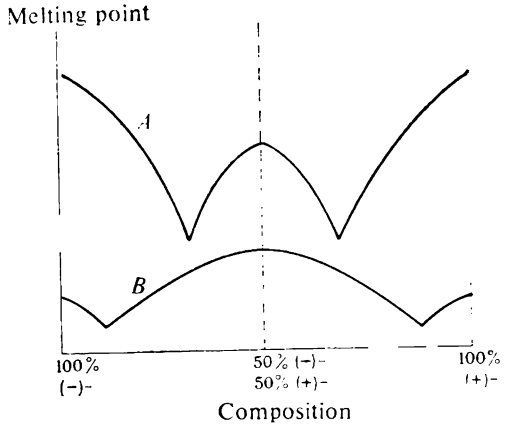

Does it represent (—)- or (+)-2-butanol? To answer this question, two interchanges must be made to bring the formula to a standard form (say, by the interchange of $CH_3$ and $C_2H_5$, and then of $C_2H_5$ and OH): it will be found that this is the formula of (+)-2-butanol (see page 47, where the (—)-antipode of 2-butanol is shown).

## 1.10. RACEMATES

Those who begin studying stereochemistry are not infrequently mistaken, believing that every substance, whose formula contains an asymmetric atom, must of necessity possess optical activity. If, however, an asymmetric centre appears during the course of ordinary reactions (a substitution in the $CH_2$ group or addition across a double bond, etc.), the probability of formation of both antipode configurations is equal. Therefore, in spite of the asymmetry of each individual molecule, the resulting compound will be found optically inactive. Such types of optically inactive modifications consisting of equal amounts of both antipodes have come to be known as **racemates.**

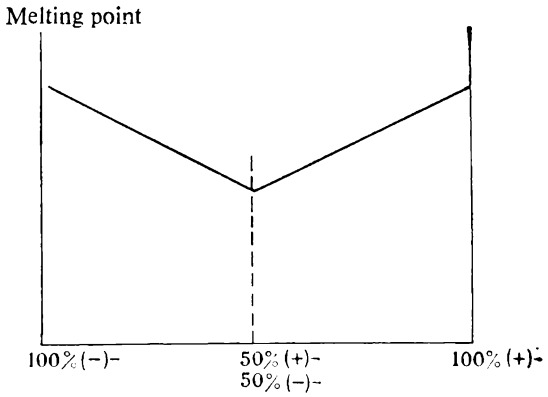
The term "racemic mixture" occasionally used in the literature is not exact. In most cases, racemates are not simple mixtures but are instead molecular compounds of optical antipodes. These **true racemates** have physical constants of their own (melting point, density, solubility), which differ from the corresponding constants of the optical antipodes. Dia-

Figure 1.22.




*Melting-point diagrams of racemates.*

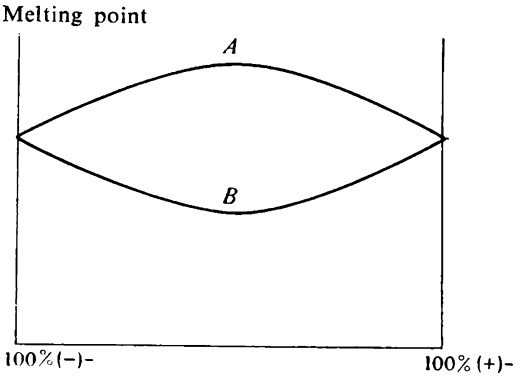
Figure 1.23.




*Melting-point diagram of a conglomerate.*

grams of melting point versus composition show that the true racemate behaves as an individual compound with a sharply distinct melting point; addition of either of the optical antipodes to it contaminates the racemate, lowering its melting point and making it less distinct. The melting

Figure 1.24.




*Melting-point diagrams of pseudoracemic mixed crystals.*

point-composition diagrams given in Fig. 1.22 show the melting behaviour of two racemates: the melting point of one of them (*A*) lies below and that of the other (*B*) above the melting points of the enantiomers.

Racemic forms may also exist as **conglomerates,** i.e., simple mixtures of separate crystals of the dextrorotatory and levorotatory antipodes. A characteristic binary phase diagram for this case is given in Fig. 1.23.

A third possible racemic modification is the existence of a continuous series of solid solutions capable of being formed at any ratio of the antipodes (Fig. 1.24). The melting-point curve may be either convex (*A*) or concave (*B*) if the (±) form is a racemic solid solution; in the ideal case, a straight line obtains.

The diagrams of melting point versus composition make it possible to identify the type of racemic modification in each particular case. This is important in one of the methods of determination of configuration.

Since ordinary syntheses lead to racemates, it is natural to ask: How are optically active substances originally formed? What is the source of these substances? An important source of such substances is living nature: optical activity is exhibited by proteins and the natural amino acids of which proteins are composed, carbohydrates, many natural hydroxy acids (tartaric, malic, mandelic), terpene hydrocarbons, terpene alcohols and ketones, steroids, alkaloids, and other compounds. The synthetic preparation of optically active substances is based on the use of two methods:

1. *Resolution of racemates*, i.e. the process whereby a racemic form is separated into the individual enantiomers (optical antipodes).

2. *Asymmetric synthesis* which involves stereospecific reactions in the course of which one of the antipodes is predominantly formed (or predominantly destroyed).

These methods will be described in Chapter 2.

## 1.11. DIASTEREOISOMERISM

Compounds with several asymmetric atoms possess important specific features which differentiate them from the simpler optically active substances with one asymmetric centre that have been considered above.

Suppose that the molecule of a certain compound has two asymmetric atoms; let these atoms be denoted as A and B. It is easy to see that molecules with the following combinations are possible:

Molecule 1 $\overset{(-)}{A}\ \overset{(-)}{B}$ Molecule 3 $\overset{(-)}{A}\ \overset{(+)}{B}$

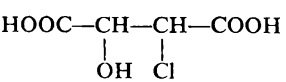
Molecule 2 $\overset{(+)}{A}\ \overset{(+)}{B}$ Molecule 4 $\overset{(+)}{A}\ \overset{(-)}{B}$

Molecules 1 and 2 constitute a pair of optical antipodes (enantiomers); the same is true of the pair of molecules 3 and 4. But if we compare the molecules from the different pairs of antipodes, 1 and 3, 1 and 4, 2 and 3, and 2 and 4, we shall see that the pairs listed are not optical antipodes: the configuration of one of the two asymmetric carbon atoms is reversed. These are all pairs of the isomers called **diastereoisomers** or more commonly, **diastereomers,** i.e., stereoisomers which are *not* enantiomers (they are not related as object and mirror image).

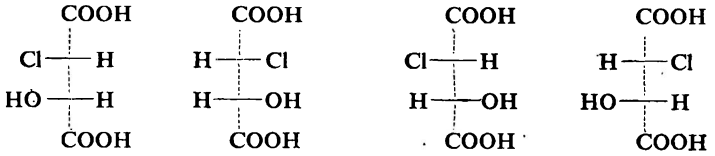
This definition allows a pair of *cis-trans* isomers to be also referred to as diastereomers: this extended definition of diastereomers has in fact been often used in the literature for the last several years.

Diastereomers differ from one another not only in optical rotation but also in all other physical constants: they have different melting and boiling points, solubilities, adsorption coefficients, etc. The differences in the properties of diastereomers are often no less than the differences in the properties of structural isomers. This circumstance makes it possible to easily separate diastereomers from each other by the usual physical methods, most often by fractional crystallization and adsorption.

An example of a diastereomeric compound is chloromalic acid



Its stereoisomeric forms have the following projection formulas:




*erythro*-Forms *threo*-Forms

The prefixes *erythro* and *threo* are derived from the names of two simple sugars, erythrose and threose, respectively. These terms are used to specify the relative disposition of substituents in compounds containing two asymmetric atoms: *erythro*-isomers are those in which two identical or similar substituents on adjacent carbons are on the same side (on the left or right in the projection formula, as the hydroxyl groups in erythrose; *threo*-isomers have identical (or similar) substituents on opposite sides of the projection formula, as the hydroxyl groups in threose.

Two *erythro*-isomers constitute a pair of enantiomers (optical antipodes) which when mixed give a racemate. The *threo*-forms are also a pair of enantiomers, which also form a racemate on mixing; the properties of the *threo*-racemate are different from those of the *erythro*-racemate. Thus, there are only four optically active isomers of chloromalic acid and two racemates. The properties of these are given in Table 1.4.

TABLE 1.4. THE PROPERTIES OF STEREOISOMERS OF CHLOROMALIC ACID

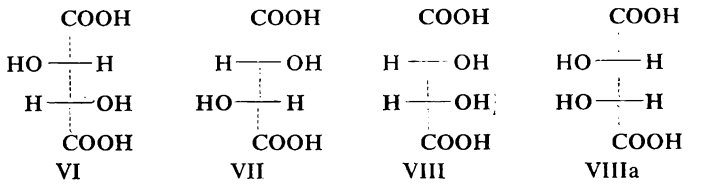
| | Formula | | | |
|---|---|---|---|---|
| | COOH<br>H—OH<br>H—Cl<br>COOH | COOH<br>HO—H<br>Cl—H<br>COOH | COOH<br>H—OH<br>Cl—H<br>COOH | COOH<br>HO—H<br>H—Cl<br>COOH |
| Name | *erythro*-(−) | *erythro*-(+) | *threo*-(+) | *threo*-(−) |
| Melting point, °C | 173 | 173 | 167 | 167 |
| $[\alpha]_D$ | −31.3* | +31.3* | +9.4** | −9.4** |
| | Racemate I (*erythro*-form) | | Racemate II (*threo*-form) | |
| Melting point, °C | 146 | | 153 | |
| Constants of diethyl ethers of *erythro*- and *threo*-racemates | $d_4^{20}$ 1.2387, $n_D^{20}$ 1.4517 | | $d_4^{20}$ 1.2321, $n_D^{20}$ 1.4507 | |

* In ethyl acetate.
** In water.

1.11. Diastereoisomerism

The number of spatial isomers increases with increasing number of asymmetric centres, each new asymmetric centre doubling the number of isomers. It is determined by the formula $2^n$, where $n$ is the number of asymmetric centres.

The number of stereoisomers may decrease because of the partial symmetry that arises in certain structures. An example is tartaric acid, the number of individual stereoisomers for which is reduced to three. Their projection formulas are as follows:

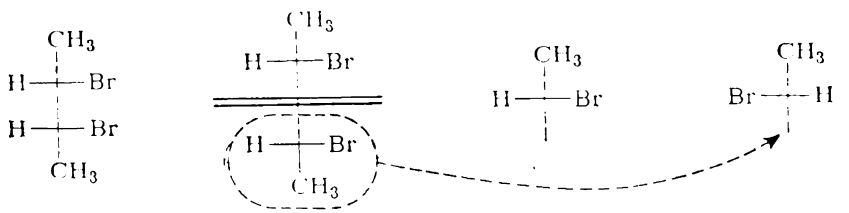



Formula VIIIa is identical with formula VIII: the former is transformed into the latter by rotation through 180° in the plane of the page and, hence, does not represent a new stereoisomer.

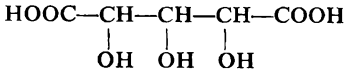
Formulas VI and VII represent the optical antipodes (a pair of enantiomers) of tartaric acid, when the antipodes are mixed, an optically inactive racemate, racemic acid, is formed.

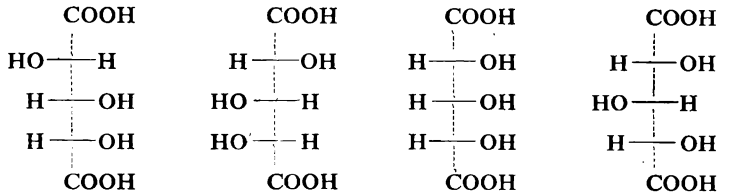
There is another, optically inactive modification for tartaric acid, the *meso*-form (*meso*-tartaric acid), represented by formula VIII. In contrast to the racemate, which can be resolved into the optical antipodes, the *meso*-form is nonresolvable: in its molecule, the configuration of one of the two asymmetric centres is reversed. The result is a kind of internal racemate with the two asymmetric atoms compensating each other on each side of the plane of symmetry (*meso*-tartaric acid is said to be internally compensated).

The *meso* forms are exhibited by all optically active compounds with several identical asymmetric centres (i.e., asymmetric centres linked to identical substituents). The projection formulas of *meso* compounds can be recognized because they can always be divided into two halves by a horizontal line; these two halves are formally identical when written on paper but in fact are mirror-images of each other:



For compounds having three identical asymmetric atoms there may exist two optically active isomers and two *meso*-forms. As an example may serve trihydroxyglutaric acid:





| IX | X | XI | XII |
|---|---|---|---|
| (+)-Antipode m.p. 128°C | (−)-Antipode m.p. 128°C | *meso*-Form A m.p. unknown | *meso*-Form B m.p. 152°C |

Racemate, m.p. 155°C

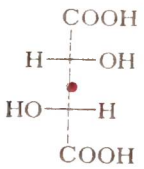
Is the central carbon atom of trihydroxyglutaric acid asymmetric or not? In formulas IX and X the central atom is clearly not asymmetric since there are structurally and configurationally identical residues at the top and bottom of the formulas. In formulas XI and XII these residues are structurally identical but they have opposite configurations. Such a difference does not give rise to optical activity (this is proved by the absence of rotation in *meso*-forms A and B) but affects the chemical properties as evidenced by the different behaviour of both *meso*-forms on heating (the *meso*-form A readily forms a lactone, whereas the *meso*-form B does not).

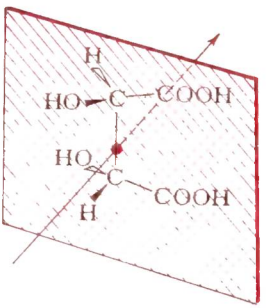
In such a molecule the central carbon atom is said to be *pseudoasymmetric*. It is transformed into a true asymmetric atom as soon as the top and bottom parts of the molecule become structurally different. Thus, for example, the acid ester of trihydroxyglutaric acid has three true asymmetric atoms and exists as eight stereoisomers.

## 1.12. ASYMMETRY AND CHIRALITY

It is only recently that the specific symmetry properties of optically active substances have drawn attention; they remained unnoticed for almost a century. The term **asymmetric** quite precisely describes the carbon

atom that carries four different substituents; here there are no elements of symmetry at all: no centre of symmetry, no axis of symmetry, and no plane of symmetry. By analogy, any optically active compound was considered to be devoid of any element of symmetry, but a more careful inspection shows that this is not the case in reality. All asymmetric molecules can exist in optically active forms, but it turns out that among optically active compounds there are compounds whose molecules are... not asymmetric! Let us consider, as an example, the projection formula of optically active tartaric acid: it has one element of symmetry — an axis of symmetry in the centre of the molecule, which passes perpendicularly to the plane of the drawing (this axis is marked with a red dot in the formula):




When rotated about this axis through 180° the formula coincides with the original one.

This example shows that optically active molecules may contain axes (but not planes and centres) of symmetry. Since the term asymmetric has thus been found to be inadequate, it has been suggested that molecules that satisfy this condition be called **chiral.** The word chiral (the Greek word *cheir* meaning hand; pronounced kīral) implies the property of "handedness", i.e., the object and mirror-image relationship of a left and right hand. It is more and more frequently used in the literature. We shall use this term in the following discussion further in the text as the need arises.

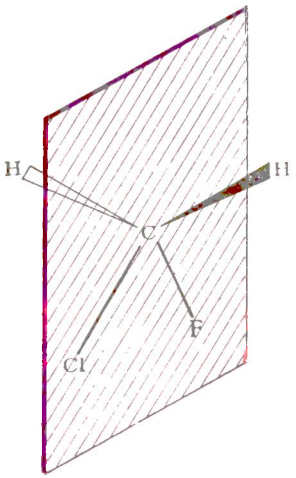
Eliel has proposed another term in his well-known book (12), namely **dissymmetric,** but this concept is used in a different connotation by other authors (13).

For the time being, let us remember that optically active substances may always be regarded as having *chiral* molecules but they must not necessarily be asymmetric.

## 1.13. THE ENANTIOTOPIC AND DIASTEREOTOPIC RELATIONSHIPS OF ATOMS AND GROUPS

With the advent of new instrumentation and methods of investigation, polarimetry has lost its dominating position in the detection of the fine differences in the spatial structure of molecules, which are responsible for the existence of optical antipodes (or enantiomers). At present, these and even more subtle differences can be recognized through the use of other techniques.

We shall consider, as the simplest example, the molecule of fluorochloromethane, $FCH_2Cl$. We may ask: Could there be found any difference between the hydrogen atoms contained in this compound?




It is seen that the hydrogen atoms differ in position relative to the plane passing through Cl—C—F: one of the hydrogen atoms is on the left from this plane, and the other on the right. These atoms are non-equivalent insofar as their positions are concerned; they are said to be **enantiotopic.**

Enantiotopic atoms (or groups) can be compared with two identical houses which stand on opposite sides of the street.

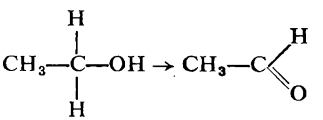
The condition for the appearance of enantiotopic atoms is the presence of a definite "direction", of a certain reference point in the system under consideration. This condition is observed in the molecule of fluorochloromethane. It disappears in difluoromethane: any of the fluorine atoms may be found to be in front of the plane of the drawing — the reference

point is not specified, and therefore the same hydrogen atom will be seen either on the left or on the right side, depending on the orientation of the molecule relative to the viewer. The hydrogen atoms in difluoromethane are completely *equivalent*.

A different approach may also be used: if we mentally replace one of the atoms (or one of the groups), we may arrive at the formula of one enantiomer (optical antipode), and when another atom is replaced, the formula of the other enantiomer is obtained; such atoms (or groups) are said to be enantiotopic.

The term enantiotopic, in principle, implies **arranged enantiomerically.** It has sense not for any one atom or group taken separately but only for a *comparison* of objects. This comparison may be made for a single molecule, as in the above example of fluorochloromethane **(internal comparison),** or for different molecules. Therefore the term enantiotopic may be applied to the corresponding pairs of identical substituents in optical antipodes, say, to the OH groups in lactic acid and to the deuterium atoms in the formulas of the optical antipodes of 1-deuteroethanol given below **(external comparison).**

The introduction of the concept of enantiotopic atoms (or groups) would be pointless if it were not possible to detect experimentally the enantiotopic differences. Such a possibility is furnished by reactions with chiral (optically active) reagents, especially enzymatic reactions, and also by physical methods, in particular, nuclear magnetic resonance spectroscopy. Thus, ethanol when acted on by the enzyme alcoholdehydrogenase is oxidized to acetaldehyde:



Experiments with labelled atoms have shown that one definite hydrogen atom of the two enantiotopic hydrogen atoms of the $CH_2$ group is removed (14).

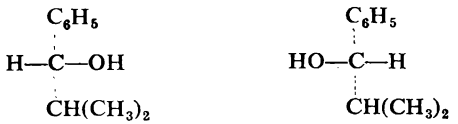
The deuterated ethanol used in these experiments exists as two optical antipodes (with a negligibly small specific rotation, amounting to hundredths of a degree):

XIII XIV

When one of the enantiomers (XIV) is reacted with alcoholdehydrogenase, the deuterium is removed from the molecule; if enantiomer XIII is made to react with the enzyme, the hydrogen is eliminated and the

deuterium is left. This means that the decisive role is played not by the nature of the atom but by its position, i.e., a difference which on conversion to the non-labelled compound turns into the enantiotopy.

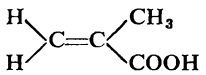
The non-equivalence of enantiotopic groups can be detected from the NMR spectra measured in chiral solvents. The methine hydrogen atoms in the optical antipodes (enantiomers) of isopropylphenylcarbinol are enantiotopic on external comparison:



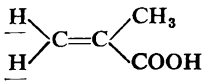
In ordinary solvents, the methine protons of both enantiomers give signals with the same chemical shift in the NMR spectra, and in chiral solvents [e.g., in (+)-1-(α-naphthyl)-ethylamine] the chemical shifts of both enantiotopic protons differ by 0.025 ppm.

The two identical atoms (or groups) occupying the enantiotopic positions in molecules that possess chirality are said to be **diastereotopic.** The replacement of one of the two diastereotopic atoms (or groups) by an atom or group of a different chemical nature gives rise to a pair of diastereomers. For instance, in 2-butanol, $CH_3$—$CH_2$—CHOH—$CH_3$, the hydrogen atoms of the methylene group are diastereotopic; this is also true of the fluorine atoms in the compound $CF_2Br$—CHBrCl.

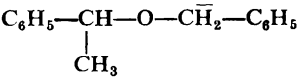
Pairs of identical atoms (groups) in ethylene compounds of the $R_2C{=}CR'R''$ type are also diastereotopic; as an example may be cited the methylene hydrogen atoms in methacrylic acid



Diastereotopic atoms (groups) differ chemically — in rates of reactions involving ordinary (achiral) reagents. Such atoms or groups can be directly detected in NMR spectra (Fig. 1.25). Below are given two examples of compounds with diastereotopic atoms (groups) with the value of $\Delta\tau$ being specified in ppm of the difference in the chemical shifts of the diastereotopic atoms (in the formulas these atoms are underlined):



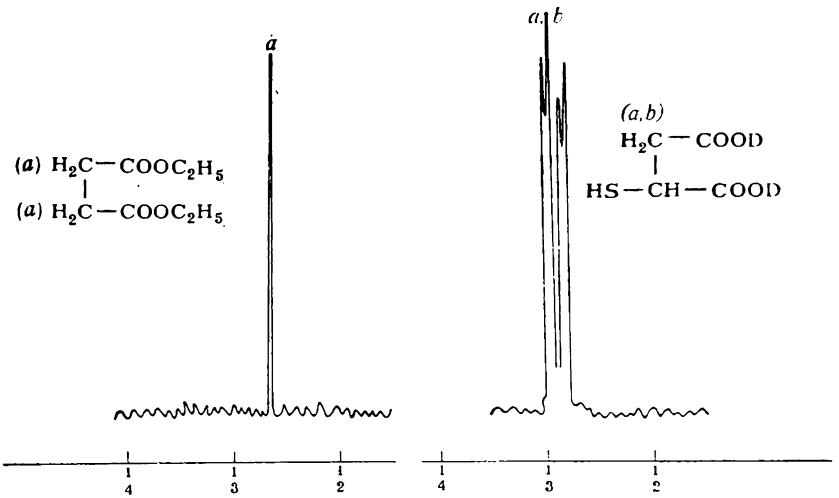
0.85 ppm



0.18 ppm

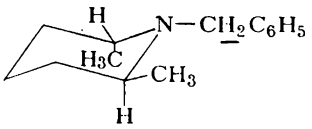
The similar behaviour of the hydrogen atoms of the $CH_2$ groups in the two compounds given above (one compound is saturated and the

Figure 1.25.

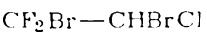



*Signals of equivalent and diastereotopic protons in PMR spectra.*

other unsaturated) is responsible for the fact that the concept of diastereotopic atoms (groups) is extended to *cis-trans* isomers. Further examples of diastereotopic atoms are:

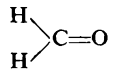



0.13 ppm

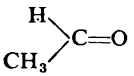



3.34 ppm

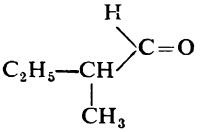
Not only substituents but the "sides" of a double bond (C=C, C=O, etc.) and free pairs of electrons may also be equivalent, enantiotopic or diastereotopic; for example, for the sides of the C=O double bond




Equivalent

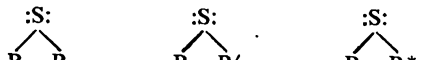



Enantiotopic

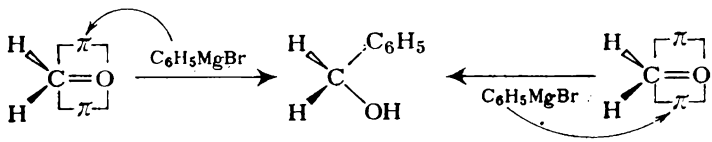



Diastereotopic

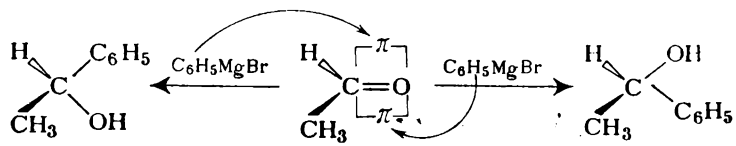
and for free electron pairs (R and R′ are achiral radicals, and R* is a chiral radical):




If we consider, for example, an organomagnesium synthesis involving a carbonyl compound with equivalent sides of the C=O double bond, we shall see that the structure formed is the same, regardless of the direction of the approach of the reagent:

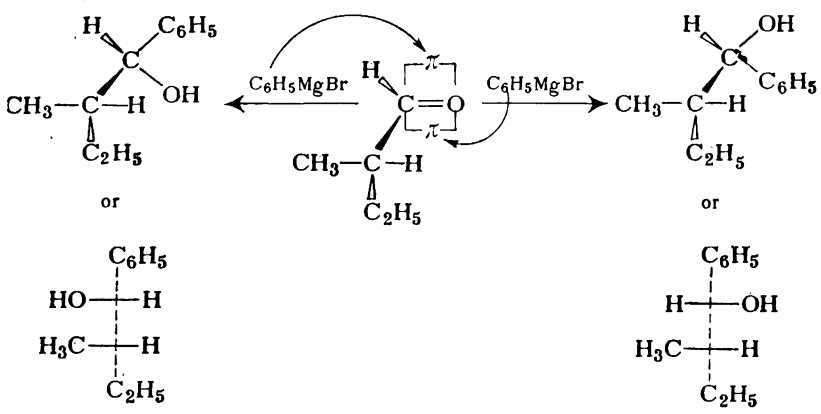



If the sides of the CO group are enantiotopic, either of the enantiomers is formed, depending on the direction of the approach of the reagent:




Since in ordinary reactions the two directions of approach are equally probable, a racemate is actually formed.

A carbonyl compound with diastereotopic sides of the CO group will give rise to a pair of diastereomers in a similar reaction:



The transition states leading to two diastereomers are, in a general case, energetically non-equivalent, and therefore the formation of diastereomeric products is not equally probable.

For a more detailed treatment of these problems, the reader is referred to articles written by Mislow and Raban (15).

## 1.14. THE SIGN OF ROTATION AND THE CONFIGURATION

The possibility of differentiating between the optical antipodes (enantiomers) is furnished primarily by measurements of optical activity. In practice, polarimetric measurements are used for this purpose so often that the existence of other differences between the enantiomers is ignored. Thus, in certain cases, the crystal shapes of the antipodes are different: one is the mirror image of the other. Also different is the behaviour of the enantiomers towards chiral reagents, especially towards enzymes.

The NMR spectra in chiral solvents are also different. As seen from this, the number of differences between the enantiomers is not small; nevertheless, the polarimetric determination of the sign of optical rotation still remains to be the most widely used procedure for identification of antipodes.

Not infrequently, those who begin studying stereochemistry get an impression that the sign of rotation is a direct expression of the configuration, i.e., the spatial arrangement of the substituents about the chiral centre. To scatter this illusion, recall that the sign of rotation of the same antipode may vary, depending on the conditions under which measurements are carried out: the nature of the solvent, concentration, temperature, the wavelength of the light.

Thus, the diethyl ether of dextrorotatory tartaric acid is a liquid with a specific rotation of $[\alpha]_{\mathrm{D}}^{0} = +7.4°$. A solution of this compound in ethyl acetate also rotates the plane of polarization to the right, $[\alpha]_{\mathrm{D}}^{20} = +10.0°$; but a solution of it in chloroform shows a rotation to the left, $[\alpha]_{\mathrm{D}}^{20} = -3.19°$. With rise of temperature the magnitude of the left-handed rotation of the solution in chloroform decreases, passes through the zero at 36°C and then becomes positive: $[\alpha]_{\mathrm{D}}^{30} = +1.26°$. The same antipode of malic acid changes its sign of rotation in aqueous solution, depending on the concentration: $[\alpha]_{\mathrm{D}}^{23} = +2.72°$ at a concentration of 64 per cent and —0.90° at a concentration of 21 per cent. An aqueous solution of aspartic acid at 20°C rotates the plane of polarization to the right, $[\alpha]_{\mathrm{D}}^{20} = +4.36°$; when the temperature increases, the plane of polarization is rotated to the left, $[\alpha]_{\mathrm{D}}^{90} = -1.86°$.

The configuration of each of the antipodes remains unchanged in all these cases. Determination of the configuration of optical (and also of geometrical) isomers constitutes one of the specific areas of stereochemistry. The experimental techniques employed for this purpose will be discussed at a later time.

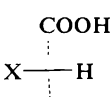
At this point, the reader must ascertain the general logic in the solution of this problem, the general setting-up of the problem, which is as follows: two isomeric compounds, X and Y, are given (several compounds in a general case), each of which is characterized by specific definite properties; these compounds are known to exhibit spatial isomerism and may have formulas A and B; it is required to determine which formula belongs to which compound, i.e., whether substance X, for example, has formula A or B (the answer to this question will automatically determine the formula of substance Y).

## 1.15. NOMENCLATURE OF OPTICAL ISOMERS

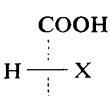
The spatial structure of optical antipodes (enantiomers or enantiomorphs) has been so far represented with the aid of drawings or Fischer projection formulas, without specifying the names of individual compounds. But formulas cannot be used in all cases — they cannot be employed in oral speech, cannot be included in the alphabetical order in dictionaries, handbooks.

Any compound, including an optical antipode, must have a name of its own; in this particular case, a name must reflect the specific features of the spatial structure of molecules.

The simplest and oldest and the most commonly used system of nomenclature of optical antipodes is based on a comparison of the projection formula of the antipode, to which a name is to be assigned, with the projection formula of some standard substance chosen as a key compound. Thus, with α-hydroxy acids and α-amino acids the key is the top part of their projection formulas (Fischer projection formulas):



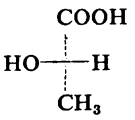

L-Hydroxy acids (X = OH)
L-Amino acids (X = $NH_2$)

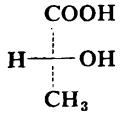


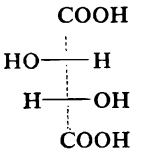

D-Hydroxy acids (X = OH)
D-Amino acids (X = $NH_2$)

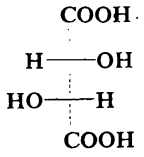
The configuration of all α-hydroxy acids that contain a hydroxyl group on the left-hand side in the Fischer projection formula is designated by

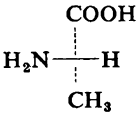
the letter L; if the hydroxyl group is on the right in the projection formula, the letter D is used. Some examples are given below:

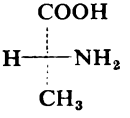

L-(+)-Lactic acid


D-(−)-Lactic acid


L-(−)-Tartaric acid

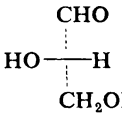

D-(+)-Tartaric acid

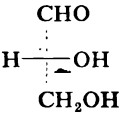

L-(+)-Alanine


D-(−)-Alanine

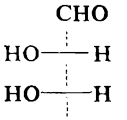
As pointed out earlier, the sign of rotation is not directly associated with the configuration: in particular, both enantiomers, dextrorotatory and levorotatory, are encountered among the D-hydroxy or D-amino acids given above.

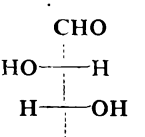
A reference compound for determination of the configurations of sugars is glyceraldehyde:

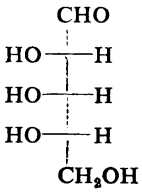

L-(−)-Glyceraldehyde


D-(+)-Glyceraldehyde

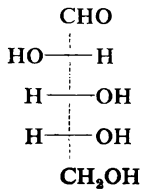
In molecules of sugars the designations D or L refer to the configuration of the *bottom* asymmetric centre:


L-(+)-Erythrose


D-(−)-Threose



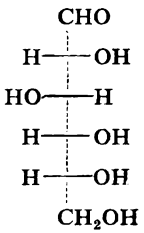

L-(+)-Ribose



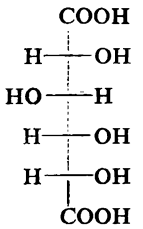

D-(−)-Arabinose

The shortcomings of this system of nomenclature are especially clearly seen from the D,L notation used for the sugars. The principal drawback is that the symbol D- or L- specifies the configuration of *only one* (bottom) asymmetric atom, while the configurations of the remaining ones are hidden in the trivial name of the compound — it must simply be memorized.

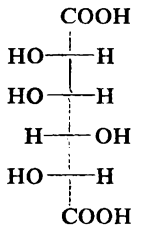
A second drawback consists in new complications that arise when one goes beyond the range of a limited steric series (a group of related compounds). Thus, for example, the dibasic (dicarboxylic) hydroxy acids, $HOOC—(CHOH)_n—COOH$, are closely related to the monosaccharides because they are the oxidation products of the latter. Therefore, it will be natural to extend the symbols used for the sugar series to those acids; for example,




D-Glucose




(*a*)

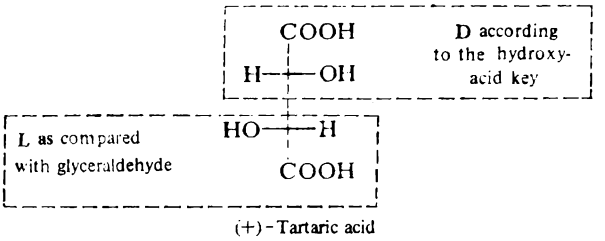



(*b*)

Saccharic acid

Considering the close relationship to D-glucose, in accordance with formula (*a*), the resulting dicarboxylic acid should be named "D-saccharic acid". The same configuration, however, may be written by turning the formula through 180° in the plane of the paper [formula (*b*)]. Then, according to the nomenclature rules for the sugars it would have to be assigned to the L-series.

Disputes have been held for a long time as regards the tartaric acids, for which different designations may be used, depending on whether the reference compound is glyceraldehyde or a hydroxy acid:

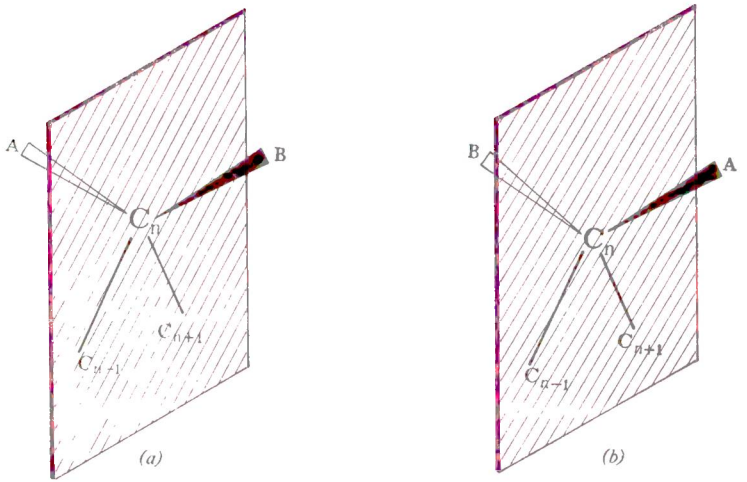



All these shortcomings of the system of reference compounds limit its application at present to three (though very important) classes of optically active compounds: sugars, amino acids, and hydroxy acids.

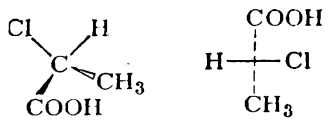
Intended for general use are the two systems of stereochemical nomenclature proposed about the same time, in the early fifties: the ρ,σ-system [the rho-sigma system, A. P. Terentiev and co-workers (8)] and the *R,S*-system [R. S. Cahn, C. Ingold, and V. Prelog (11)]. Both systems are based on the tenet that the *three-dimensional model* rather than the projection formula must be specified. Even a simplest compound with one asymmetric atom may have as many as twelve projection formulas (see above, page 47); therefore, the elaboration of stereochemical nomenclature on the basis of projection formulas requires thoroughly worked-up rules of writing such formulas for the various compounds. Consideration of a single model instead of a large variety of possible projection formulas simplifies the matter. The approach to the solution of the problem of describing a three-dimensional model is also the same in both systems; first the priority sequence is determined for the substituents at the asymmetric centre and then a designation is selected in accordance with special rules.

The main difference between the two systems is in the determination of priority. The rho-sigma system entirely rests on the priority used in building structural names, to which is added a stereochemical descriptor. In building structural names it is necessary to choose the main chain and to renumber its atoms — this gives, in principle, two coordinates (resembling polar coordinates) which specify the position of the substituent in the plane. A third coordinate (the ρ, σ designation) must be added to specify the three-dimensional arrangement.

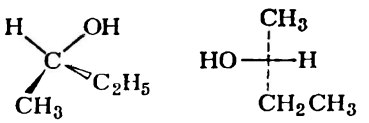
Recall what difference between two enantiotopic hydrogen atoms could be recognized by the viewer when looking at the molecular model of fluorochloromethane (see page 57): the difference is that one of the hydrogen atoms is to the right, and the other to the left. It is this difference which is used to designate the configuration. Let us arrange a perspective projection so that the beginning of the chain projects forward towards the viewer and the end of it is behind the plane of the paper.




The three-dimensional models of optical antipodes (*a*) and (*b*) have, in the adopted orientation, a mirror-image arrangement of substituents A and B (these substituents will always be different, otherwise the atom will not be asymmetric!). The position of the substituent on the left is denoted by the symbol ρ (rho), and the position on the right, by the symbol σ (sigma). This notation is included in the structural name, being added to the numeral which indicates the position of the corresponding substituent (A or B). It is easy to see that the analogous arrangement of the substituents will be seen by the viewer in going along the projection formula in the order of numbering; thus, the ρ,σ designation is easy to choose by the projection formula too. For example:



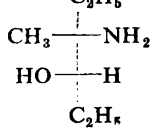

ρ2-Chloropropionic acid




σ2-Butanol

It is known that the nomenclature of organic compounds is not unambiguous; many complex compounds have several names which may differ in the order of numbering and in the main chain selected. But this does not give rise to uncertainty in the construction of projection formulas

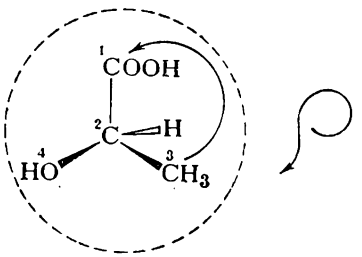
according to names, and it is this purpose that is to be achieved by the stereochemical nomenclature. For example:



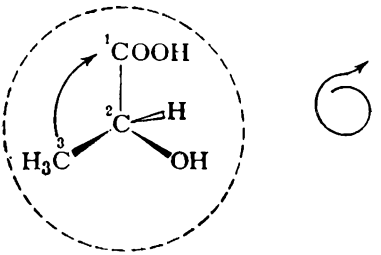

ρ3-Amino-3-methyl-σ4-hexanol
3-Amino-σ3-methyl-σ4-hexanol
ρ3-Hydroxy-4-methyl-σ4-hexylamine
ρ3-Hydroxy-ρ4-methyl-4-hexylamine

The outwardly dissimilar names listed above allow a correct projection formula of a stereoisomer to be drawn.

The symbols ρ,σ have been selected arbitrarily, meaning that they will not be used for other purposes in the nomenclature of organic compounds (unfortunately, both letters, and exactly in that combination are employed in the Hammett equation!). These designations may be tied up with the following mnemonic rule based on the asymmetric atom being viewed in another projection. This projection is reminiscent of the Newman projection based on the $C_a$—H bond (or a low-ranking substituent other than hydrogen). Let us write formulas for the antipodes of lactic acid in that projection:




The configuration is designated by the letter ρ: movement in a counterclockwise direction in going around the circle from the atom of the main chain with a higher atomic number to the atom of the main chain with a lower atomic number (from the end of the chain to its beginning); this is to be associated with the motion of the hand in writing the letter ρ.

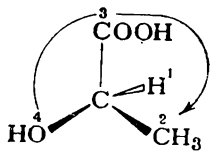



The configuration is designated by the symbol σ: movement in a clockwise direction in going around the circle from the atom of the main chain with a higher atomic number to the atom of the main chain with a lower atomic number (from the end of the chain to its beginning); this is to be associated with the same motion of the hand in writing the letter σ.

The second method of determination of the ρ,σ notation is expounded in a different way than in the earlier publications in order to make it closer to the *R,S*-

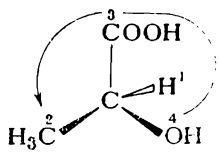
system discussed below. For other methods of determination of designations and also for additional rules the reader is referred to the literature (8, 9).

The *R,S*-system differs from the above-described ρ,σ-system only in the order of the determination of the relative priority of the substituents at the asymmetric atom. For this purpose, use is made of the sequence rule, according to which the groups are arranged in a sequence of decreasing atomic number of the atoms by which they are bound to the asymmetric carbon atom; this rule has already been considered in connection with the *Z,E*-nomenclature of geometrical isomers (see page 35). The model is drawn in just the same way as was done in the case of the lactic acid molecule for specification of the ρ,σ-designations (i.e., the substituent of lowest priority is below the plane of the paper; here and in the subsequent examples the numbers 4, 3, 2, 1 signify the order of decreasing priority of the substituents according to the Cahn-Ingold-Prelog convention):




*R*

The symbol *R* indicates the clockwise sequence of decreasing priority of atomic numbers (just as in writing the top portion of the letter *R*).

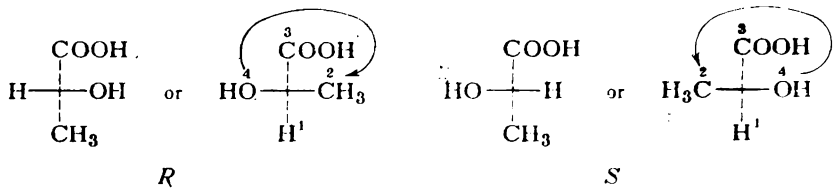



*S*

The symbol *S* indicates the counterclockwise sequence of decreasing priority of atomic numbers (just as in writing the top of the letter *S*).

To select the *R,S* symbols according to the projection formula, Cahn, Ingold, and Prelog suggest arranging substituents, by means of an even number of transpositions (which, as we already know, do not change the stereochemical meaning of the formula), in such a manner that the one of lowest priority (this is usually hydrogen) is at the bottom of the projection formula. When the sequence (decreasing priority) of the other three substituents is clockwise, symbol *R* (from the Latin *rectus*, meaning right) is used to denote the configuration, and when the sequence

is counterclockwise, the symbol *S* (from the Latin *sinister*, meaning left) is used:



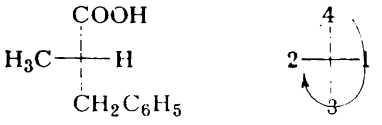

The detailed rules of the *R-S* nomenclature contain a number of additional conditions.

It is not invariably a simple matter to visualize the model in the required form or to transform the projection formula: this is especially true if we are dealing with compounds containing several asymmetric centres and cyclic structures. It will therefore be helpful if we supplement the Cahn-Ingold-Prelog procedures for assignment of *R* and *S* with another approach that will allow us to use an untransformed projection formula or model in any orientation:

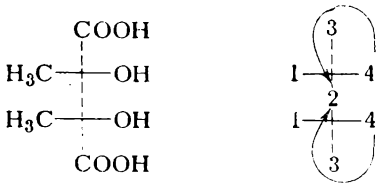
1. In assigning a configurational symbol according to the projection formula, in which the substituent of lowest priority is at the bottom or top, or according to the model with the "odd" substituents (1 or 3) being remote from us or with the "even" substituents protruding towards us, use is made of the ordinary Cahn-Ingold-Prelog rule: *R* indicates the decrease of priority in a clockwise direction, and *S* signifies the same in a counterclockwise direction.

2. In assigning the symbols according to the projection formula, in which the substituent of lowest priority is to the left or right, or according to the model with the "even" substituents (2, 4) or with the "odd" substituents (1, 3) the conversion rule is used: the clockwise sequence of decreasing priority is denoted by *S* and the counterclockwise sequence by *R*.

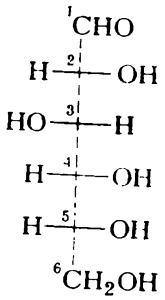
Some examples are the following:



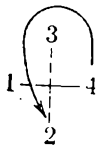

*S*-α-Methylhydrocinnamic acid



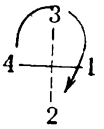

*R*,*S*-2,3-Dimethyltartaric acid



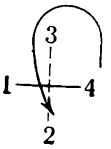

D-Glucose



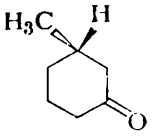

*R* at C-2



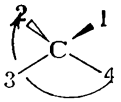

*S* at C-3




*R* at C-4 and C-5

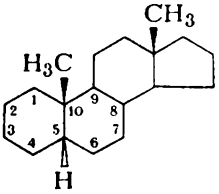



or

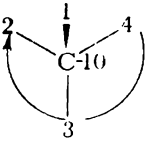



*S* according to conversion rule (group of lowest priority is in front)

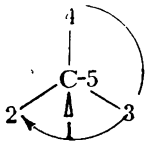
*S*-3-Methylcyclohexanone




5*R*,10*S*-10,13-Dimethylcyclopentanoperhydrophenanthrene

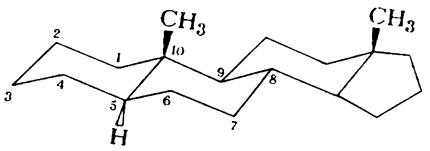



*S* at C-10 is specified according to conversion rule (group of lowest priority is in front)




*R* at C-5 is specified according to sequence rule (group of lowest priority is remote)

The last formula may be written in a different way, but in this case too the assignment of configuration (*R* or *S*) is the same:




The *R-S* system has been included in the IUPAC nomenclature rules (16).

## 1.16. THE SPATIAL STRUCTURE OF RINGS

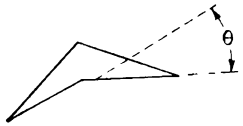
The stereochemistry of cyclic structures is largely determined by two specific features. First, in rings we have to deal with all the gradations of conformational mobility. Cyclopropane is a rigid system which differs little stereochemically from the carbon-carbon double bond. On the other hand, large rings (12-membered and larger) differ little in conformational mobility from the aliphatic chains. Between these extreme points is an interesting group of rings with a partial conformational mobility specific to each particular representative of the series. It is therefore not surprising that the conformational problems are of special importance here.

Second, the two principal types of spatial isomerism, geometrical and optical, which are encountered separately in the acyclic series, may occur *simultaneously* in cyclic compounds of definite structure. However, before we take up these problems it is necessary to be acquainted with the three-dimensional structure of the rings themselves, regardless of the substituents present.

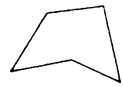
The carbon skeleton of the simplest alicyclic compound, cyclopropane, is an equilateral triangle with valence angles of 60°. This angle differs considerably from the normal value characteristic of the tetrahedral disposition of the valence bonds at the carbon atom in a state of $sp^3$-hybridization (109°28′). The bond angles at carbon atoms in cyclobutane and cyclopentane must also inevitably deviate from the normal value (characteristic of the tetrahedral structure). This specific feature of cyclic structures was noted at the close of the last century by A. Baeyer in his "strain theory". In our days, it is also believed that the deviation of valences from their normal position is unfavourable and sets up a "strained"

condition in the molecule, i.e., increases a reserve of energy in it and thereby lowers its stability. The angle strain (also known as Baeyer strain or classical strain), however, is now considered to be only one of the factors responsible for the increase of the internal energy of the molecule. There are other steric factors: the Pitzer strain (or torsional strain) — the forced deviation from the most favourable staggered conformation; the Prelog strain which signifies intramolecular van der Waals forces (mutual repulsion of the atoms brought closer together, mainly hydrogen atoms); the bond opposition strain — a decrease or increase of the normal interatomic distances (bond lengths). Any molecule, including a cyclic one, tends to adopt such a spatial form in which the sum of all these strains (internal energy included) is at a minimum.

With a planar arrangement of the ring carbon atoms, only unfavourable eclipsed conformations are possible. Therefore the three-membered ring is the only one, whose carbon atoms lie in the same plane (for the simple reason that a plane can always be drawn through three points). All other rings, beginning with the four-membered one, have a non-planar structure. Thus, cyclobutane has a square form, which is somewhat bent along the diagonal XV (the folding angle θ is several tens of degrees). The most stable form of cyclopentane is the envelope XVI:




XV



XVI

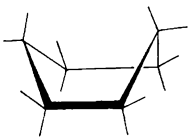
Because of the non-planar structure the Pitzer strain is lowered, and the angle strain in cyclobutane remains to be considerable, while in cyclopentane it is very low.

The angle of departure of the valences, α, in planar rings from their normal (tetrahedral) position is calculated from the formula

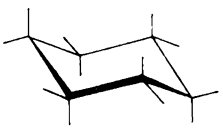
$$\alpha = \frac{1}{2}\left[109°28' - \frac{2(n-2)}{n} \times 90\right]$$

where $n$ is the number of members in the ring. For cyclopropane this angle is 24°44′, for cyclobutane, 9°44′, and for cyclopentane, 0°44′.

A six-membered ring can be constructed in two forms having no angle strain — either in the boat form, XVII, or in the chair form, XVIII:



XVII

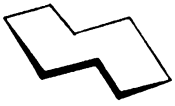


XVIII

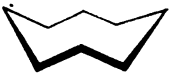
The energy of the boat form is higher, partially because the two pairs of carbon atoms (at the bottom of the boat) are in the eclipsed conformation. In the chair form all the conformations are staggered, and the internal energy is lower. Therefore, compounds of the cyclohexane series exist, as a rule, in the chair form.

The chair conformation is also characteristic of compounds of the cycloheptane series, XIX; apart from the chair form XX, cyclooctane may also exist in the crown form XXI:

XIX



XX



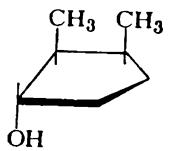
XXI

Nine-, ten-, and eleven-membered rings too have their own preferred conformations. Beginning with a 12-membered ring, the conformational mobility becomes so high that it is difficult to fix any of the preferred conformations.

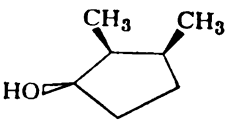
## 1.17. GEOMETRICAL AND OPTICAL ISOMERISM IN THE ALICYCLIC SERIES

As has already been pointed out, the presence of substituents — side carbon chains or functional groups — may give rise to geometrical and optical isomers in the alicyclic series. Before taking up the discussion of these problems it is necessary to agree about methods of representation of the three-dimensional (spatial) structure of substituted cyclic systems

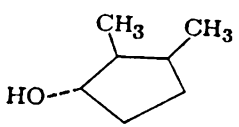
on paper. The alicyclic nucleus is most often pictured, by convention, in the form of a planar polygon, the ring (skeletal) carbon atoms and the hydrogen atoms attached to these carbon atoms being omitted. For the spatial arrangement of the substituents to be written, the polygon is considered to be perpendicular to the plane of the paper and the substituents to be at the top and bottom parts (*a*) or the ring is arranged in the plane of the page and the positions of the substituents above or below this plane are indicated, respectively, by solid or light wedges (*b*) or by heavy and broken bonds (*c*):



*(a)*



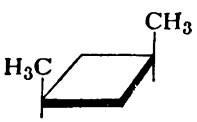
*(b)*



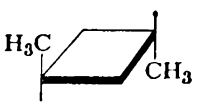
*(c)*

Though the representation of the ring in both methods is planar, it is well known that this is not the case in reality. In many cases, not only the arrangement of the substituents but the spatial structure of the ring itself must be reflected more exactly; here one makes use of the various perspective formulas which will be discussed at appropriate places in the book.

**Geometrical isomerism** similar to the isomerism of ethylene compounds arises in three-, four-, and five-membered rings having at least two substituents at different carbon atoms. A rigid ring plays the same role as the double bond in ethylene compounds: the substituents may be arranged on the same side of the ring or on opposite sides of it. For example, for 1,3-dimethylcyclobutane:



*cis-*

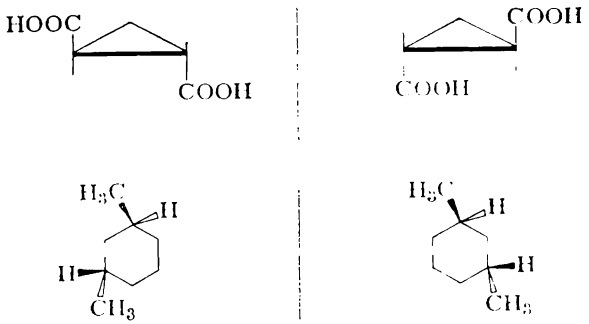


*trans-*

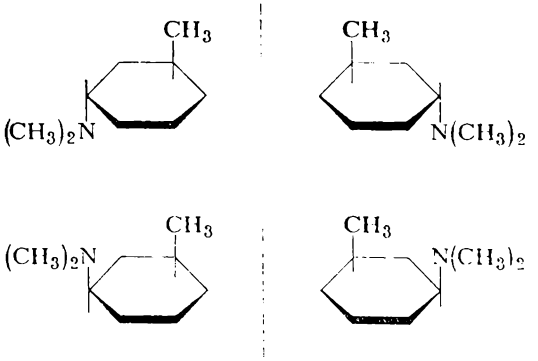
The fact that the cyclobutane ring is not planar does not change the picture under consideration. Not some definite carbon atom is brought out of the plane, but any of them may in its turn occupy this position.

*Cis-trans* isomers analogous to those considered above also exist for

disubstituted cyclopropanes and cyclopentanes. But in this case the *trans*-form will have no elements of symmetry and will become capable of existing as a pair of optical antipodes (enantiomers). The same behaviour is displayed by unsymmetric di- and polysubstituted derivatives of *any* cycloalkane. For example, for *trans*-cyclopropane-1,2-dicarboxylic acid and *trans*-1,3-dimethylcyclohexane:

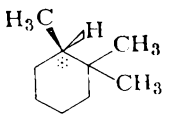


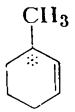

The presence of two *dissimilar* unsymmetrically arranged substituents leads to the appearance of *two* pairs of optical antipodes, in which case not only *trans*- but also the *cis*-form is asymmetric. For example:

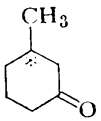


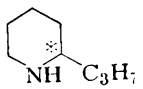

In all the examples given we are dealing with compounds having two chiral centres, the *cis*-isomer being basically an inactive *meso*-form (due to intramolecular compensation) if the substituents are identical. For optically active cyclic compounds to be produced, *one* chiral centre

will suffice if the ring itself is found to be unsymmetric due to substitution, a double bond, a carbonyl group or a hetero atom. For example:

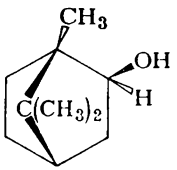


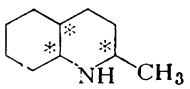




In bicyclic systems, the key atoms become asymmetric as soon as there appears any substituent arranged unsymmetrically with respect to these atoms. For example, XXII is one of the optically active forms of the terpene alcohol borneol (there exist a total of four optical isomers)




XXII



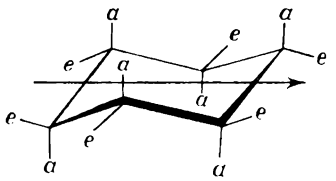

XXIII

As a further example may be cited 2-methyldecahydroquinoline (XXIII) which contains three asymmetric centres; this compound may exist as eight optical isomers.

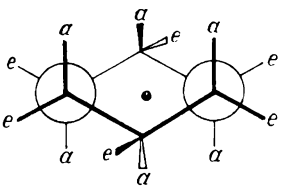
Compounds of the cyclohexane series are capable of displaying the same types of spatial isomerism, geometrical and optical, just as in the case of rings with a smaller number of members. But, in contrast to $C_3$-$C_5$ rings, in cyclohexane the essential part is played by the non-planar form of its ring and the conformational problems assume special importance.

Substituents linked to the cyclohexane ring in the chair form may occupy two non-equivalent positions, the axial (*a*) and the equatorial

(*e*) position (the arrow is the axis required to draw a projection of the Newman projection formula type):




The substituents in these positions interact differently with neighbouring atoms: in the equatorial position the substituent arranges itself "more freely", the interference of the adjacent atoms being less. This is especially clearly seen in the projection in which two pairs of adjacent ring carbon atoms are disposed one after the other (just as in Newman formulas):

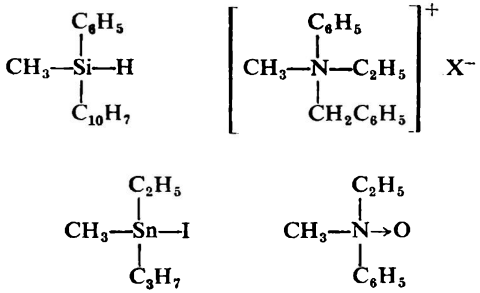



The axial substituents are in the skew conformation relative to the adjacent C—C bonds of the ring, while the equatorial substituents are in the more favourable transoid conformation. Besides, the axial substituents are found to be closer to the axially oriented hydrogen atoms at carbon atoms in positions 3 and 5 with respect to the substituent. Such 1,3-*syn*-diaxial interactions are also unfavourable. The outcome of all this is that the internal energy of the molecule with the equatorial arrangement of the substituent is lower than in the case of the axial arrangement.

## 1.18. TYPES OF OPTICALLY ACTIVE SUBSTANCES

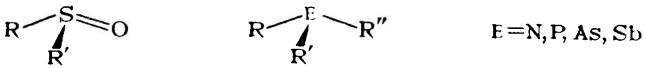
The carbon atom is not the only atom that creates chiral centres in the molecules of organic compounds. Silicon and tin and the tetracovalent

nitrogen atom in quaternary ammonium salts and the oxides of tertiary amines may also be a chiral centre:

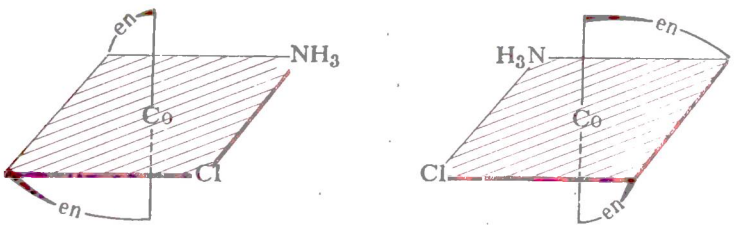


In these compounds, the centre of asymmetry has a tetrahedral configuration, just like an asymmetric carbon atom. There are, however, compounds with the chiral centre having a different spatial structure.

The *pyramidal* configuration is assumed by chiral centres formed by trivalent nitrogen, phosphorus, arsenic, antimony, sulphur. To this type of optically active compounds belong certain derivatives of trivalent nitrogen, phosphines, arsines, stibines, sulphoxides.

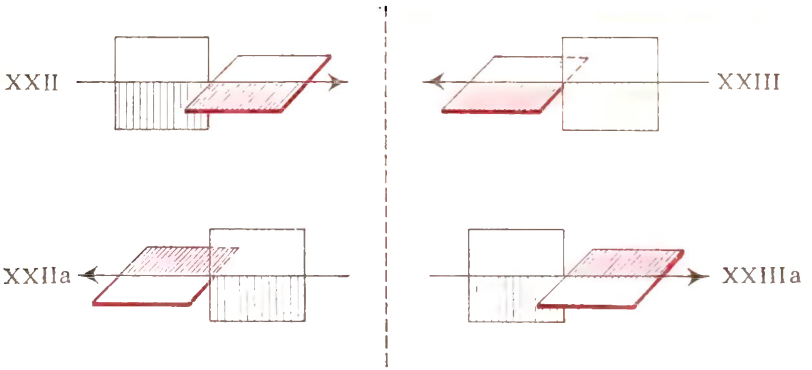


The *octahedral* configuration is characteristic of optically active complex compounds. As an example, we may cite optically active complexes formed by cobalt with ethylene diamine (designated as "en" in the formulas given below):

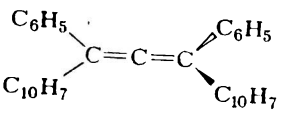


Optically active complexes with the octahedral configuration are also known to exist for chromium, iron, aluminium, ruthenium, rhodium, iridium, platinum, arsenic.

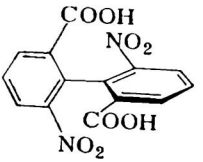
All the optically active compounds so far considered had a **chiral centre** in the form of an asymmetric carbon atom or other atoms (silicon, nitrogen and its analogues in the Periodic System, and also sulphur, metals). Optical activity may however arise in the absence of a chiral centre, due to the chirality of the structure of the molecule as a whole. In such cases we speak of molecular chirality (molecular asymmetry or dissymmetry). The types of molecular asymmetry are varied; we shall discuss them in more detail throughout the text; for the present we shall confine ourselves to considering some of the most typical examples. In these examples, the geometrical factor responsible for optical activity is either the **axis of chirality** or the **plane of chirality.** These concepts are not so easy to define; it would be better if we illustrate them with an example. Two antipode axes of chirality are presented on the diagrams XXII and XXIII. The observer moving from left to right along the diagram XXII in the direction of the axis shown by an arrow will first see a dark field below and then on the right-hand side. When moving back the observer will see the same arrangement of the dark fields (the entire picture has to be turned 90° along the axis of chirality in a clockwise direction, which gives the orientation shown in XXIIa). The diagrams XXIII and XXIIIa represent the antipode axes of chirality:




Examples of compounds with an axis of chirality are optically active allene XXIV and an optically active derivative of diphenyl (biphenyl) XXV:

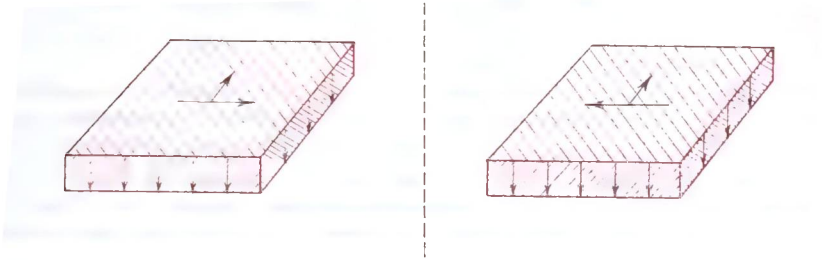



XXIV



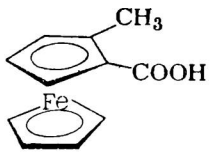

XXV

The **plane of chirality** is characterized by the presence of the top and bottom parts and also of the right- and left-hand sides. Two enantiomeric planes of chirality are shown below (the arrows represent certain directions that can be fixed in the molecule and which allow us to distinguish the top from the bottom of the plane of chirality):



As examples of compounds having a plane of chirality may be cited optically active *trans*-cyclooctene XXVI and an optically active derivative of ferrocene, XXVII:

XXVI




XXVII

## 1.19. STEREOCHEMICAL SPECIFICITY OF REACTIONS

At present the principal area of stereochemistry (as to importance and scope) is dynamic stereochemistry which deals with the influence of the spatial structure on the rate and direction of chemical reactions. The problems of dynamic stereochemistry will be treated throughout the text; for the present it is necessary to recall some of the main concepts from the general course of organic chemistry.

The result of substitution reactions taking place at the asymmetric centre atom is intimately connected with the mechanism of the reaction. Ingold formulated two rules for nucleophilic substitution reactions:

**Rule for $S_N2$ reactions:** the substitution at an asymmetric atom, which occurs by the bimolecular mechanism $S_N2$, is invariably accompanied by inversion of configuration, independently of the details of the structure of the molecule.

**Rule for $S_N1$ reactions**: the substitution at an asymmetric atom, which takes place by the unimolecular mechanism $S_N1$, is usually accompanied by racemization or partial inversion of configuration. The same reactions, however, may occur with retention of configuration if the molecule contains a configuration-protecting group.

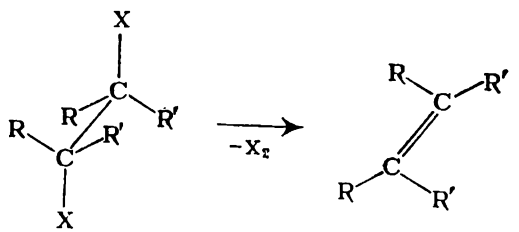
Configuration-protecting groups include first of all the carboxyl group and also a number of weakly nucleophilic groups, such as OR, OCOR, $NHCOC_6H_5$, etc., which are attached to the carbon atom adjacent to the atom being replaced.

The stereochemistry of free-radical and electrophilic substitution reactions has been studied to a lesser extent. The "normal" result of electrophilic substitution reactions is probably *retention of configuration*.

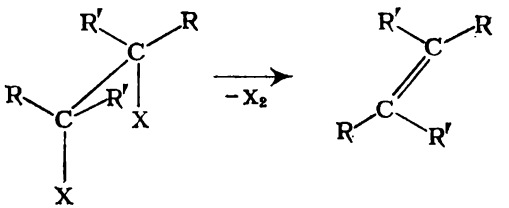
The stereochemical result of substitution reactions at the olefinic carbon atom can be predicted by the **Nesmeyanov-Borisov rule**: electrophilic and free-radical reactions at the olefinic carbon atom occur with retention of geometrical configuration.

The result of nucleophilic substitution reactions at the olefinic carbon atom has been determined less definitely: these reactions may proceed both with retention or inversion of configuration.

The stereochemical condition for elimination reactions taking place by the E2 mechanism is that all the four centres participating in the reaction (the two carbon atoms between which a double bond is formed and the substituents X and Y to be eliminated) be arranged in the same plane. This is achieved either with the groups to be eliminated being in the transoid ($\varphi^3$) orientation




or in the cisoid ($\varphi^0$) orientation:



With the starting compounds being suitably chosen (for example, in the case of compounds containing two asymmetric atoms) the transoid or cisoid elimination leads to different stereoisomeric forms of the reaction product.

Another mechanism of elimination reactions, E1, is less stereospecific.

*Additions* to multiple bonds may take place by the *cis*- or *trans*-addition scheme.

Dynamic stereochemistry is also concerned with problems such as the influence of spatial structure on reaction rates (steric hindrances), on the direction of electrophilic substitution reactions in the aromatic ring (shielding of *ortho*-positions), and on the occurrence of stereodirected reactions with the purpose of obtaining definite spatial forms.

The stereochemistry of reactions will be treated in more detail in chapters devoted to individual classes of compounds.

## 1.20. CLASSICAL AND MODERN STEREOCHEMISTRY

The composition of most inorganic compounds specifies their molecular structure in an unambiguous manner: $H_2SO_4$ invariably implies sulphuric acid; $Na_3PO_4$ always signifies sodium phosphate; $KAl(SO_4)_2$ always designates potassium alums, etc. In organic chemistry, the phenomenon of isomerism is widespread — there exist various compounds having the same molecular composition. Empirical summary formulas therefore become ambiguous for organic molecules: the simple formula $C_2H_6O$ represents ethyl alcohol and dimethyl ether; more complex empirical formulas may correspond to tens, hundreds and even thousands of different compounds. With the development of Butlerov's theory of chemical structure it became clear that isomers differ from one another by the order of the chemical bond between atoms — by chemical structure. Determination of chemical structure and elucidation of a structural formula has been (and remains to be) the principal task in investigations of organic compounds.

Stereochemistry originated about a hundred years ago as a natural extension of Butlerov's theory of chemical structure, as a three-dimensional representation of the planar concepts of a definite ordering of atoms in organic molecules. An immediate impetus to the development of stereochemical conceptions was the necessity to explain the existence of isomers, which could not be accounted for by the difference in chemical constitution.

It was in the attempt to interpret the nature of such isomers, mirror-image and geometrical isomers, that J.H. van't Hoff developed the concept of the tetrahedral carbon atom in 1874. The *only* method of detect-

ing mirror-image isomers was optical activity. Thus, the investigation of optically active compounds became one of the most important areas of stereochemistry. Together with the study of geometrical *(cis-trans)* isomerism it constituted the main subject matter of static stereochemistry which is concerned with study of the relationship between the three-dimensional structure of compounds and their physical properties.

The birth of stereochemistry showed that in certain cases even the structural formula could not characterize an organic compound completely: for stereoisomers to be characterized it is necessary to know their spatial configuration. Historically, the term "configuration" as originally introduced into organic chemistry was a rather limited concept. The configuration is defined as the spatial arrangement of substituents around the centre, which makes possible the existence of mirror-image forms, or as the spatial disposition of substituents relative to the $\pi$-bond or the ring. Thus, a knowledge of configuration is not entirely tantamount to the unravelling of the exact three-dimensional structure of the molecule as a whole: it refers only to the above-mentioned "particular points" in the molecule.

The use of new physical methods of investigation has enabled us to get a considerably deeper insight into the three-dimensional structure of molecules and to disclose new, hitherto unknown specific features. The most important of these was the concept of rotational isomerism (conformation) of organic molecules. On this concept was based the interpretation of most of the observations made in both static and dynamic stereochemistry.

The discovery in 1895 by P. Walden of the phenomenon, which is now known as the **Walden inversion,** was the first observation ever made in the field of dynamic stereochemistry—the stereochemistry of reactions. This was the beginning of the study of the influence of the spatial structure on the reactivity of compounds, i.e., on their chemical properties. It is dynamic stereochemistry that developed most rapidly in the succeeding decades and took up the leading position in this branch of science.

The outcome of all this was that the study of the "particular points" in the molecule (the spatial configuration around asymmetric carbon atoms or double bonds) was superseded by the study of the three-dimensional structure of the molecule as a whole. Determination of optical activity has also ceased to be of exclusive importance: it has become one of the numerous tools for the investigation of stereochemistry in general. Modern stereochemistry owes its development to the wide use of physicochemical methods of investigation.

It has already been mentioned that **X-ray** and **electron diffraction techniques** provide the most direct information about the geometry of molecules — the interatomic distances (bond lengths) and valence angles. The vectorial character of **dipole moments** allows us to draw important conclusions concerning the orientation of polar bonds. Less direct but

practically very valuable and widely employed stereochemical information is supplied by **ultraviolet** and **infrared spectroscopy.**

The most important method of investigation in organic chemistry in general and in stereochemistry in particular is **nuclear magnetic resonance.** Stereochemical information can be obtained both from the values of chemical shifts and the spin-spin coupling constants.

Data provided by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy lie at the basis of determination of many quantities characterizing the energetics of spatial isomers and conformers. The energy characteristics of isomeric compounds are also obtained by direct determinations with the aid of **thermochemical methods.**

Two closely related optical methods — **optical rotatory dispersion** (ORD) and **circular dichroism** (CD) — differ from those mentioned above by the fact that they are used almost exclusively for stereochemical purposes. Thus, practically only these methods (in conjunction with ordinary polarimetry) make it possible to differentiate between optical antipodes (enantiomers) and also, in general, between optically active and racemic forms. Optical rotatory dispersion and circular dichroism curves are especially sensitive to changes in the spatial structure of molecules. For example, the UV spectra of ketones of any structure are practically of the same nature — they are all characterized by the absorption band of the carbonyl chromophore in the region of 300 nm. The character of the ORD curves of optically active ketones is largely dependent on the *environment* of the chromophore — on the structure of the entire molecule and, primarily, on the distance between the chromophore and the asymmetric centre.

The theoretical arsenal of modern stereochemistry includes the various versions of quantum-chemical calculations which make it possible to arrive at the most favourable spatial forms of molecules and to calculate their energy parameters. A generalized topological approach to stereochemical problems has become increasingly important in recent years (17).

Summing up, it may be said that classical stereochemistry was mainly concerned with study of the structure and properties of stereoisomers (optical and geometrical). Modern stereochemistry deals with the spatial structure of molecules (independently of the existence of stereoisomers!) and with the influence of this three-dimensional structure on the physical, chemical and physiological properties of compounds.

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CHAPTER 2

# Methods of Preparation of Stereoisomers

## 2.1. INTRODUCTION

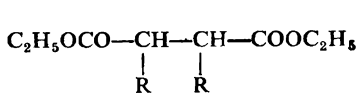
Preparation of pure stereoisomeric forms is an indispensable part of many stereochemical investigations. Only after this problem has been solved may further steps be undertaken — the study of the physical properties of stereoisomers and of their chemical reactions. But ordinary chemical reactions, as a rule, give rise to mixtures of stereoisomers — *cis-trans* forms, diastereomers or optical antipodes (enantiomers). For pure stereoisomeric forms to be obtained, such mixtures must be resolved. Another route to the preparation of pure stereoisomers is furnished by stereospecific reactions, which involve the formation of the desired stereoisomer free from impurities of other forms.

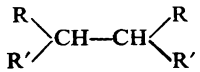
Since *cis-trans* isomers and also diastereomers differ in physical properties, the separation of their mixtures presents no formidable difficulties. For this purpose use is made of differences in solubility (separation by recrystallization), in boiling point (distillation), and in adsorbability (separation effected by means of various chromatographic techniques).

It is well known, for example, that the geometrical isomers — fumaric and maleic acids — differ greatly in water solubility: the solubility of maleic acid in water is 100 times that of fumaric acid. Obviously, these acids are easy to separate from each other by means of crystallization. Diastereomeric compounds, such as *meso*- and (±)-forms of α,β-dibromoglutaric acids, also differ strongly in water solubility: the racemate can be extracted from the mixture with boiling chloroform, the less

soluble *meso*-isomer being left in the residue (1). For the *threo*- and *erythro*-forms of 3-methylmalic acid to be separated from each other, advantage was taken of the fact that the solubilities of the barium salts of the two diastereomeric forms are different (2).

Thin-layer chromatography over silica gel has been employed by Bulgarian scientists (3) who succeeded in separating the *threo*- and *erythro*-isomers of compounds of the general formula Ar—CHX—CHY—Ar, where X and Y are different polar groups (the amino, hydroxyl and carboxyl groups in the free or modified form). The *meso*- and racemic forms of esters of aliphatic dicarboxylic acids or hydrocarbons





emerge at different times when they are separated by means of gas-liquid chromatography (4).

Generally, the preparation of pure *cis-trans* isomers or diastereomers is not an invariably easy experimental task, but in principle it does not differ from the ordinary isolation of any organic compounds in an individual form.

In contrast to this, the preparation of optically active substances is a specific task which requires the use of special techniques. The point is that optical antipodes (or enantiomers) *do not differ* from one another in boiling point, solubility and adsorbability by ordinary adsorbents. Thus, neither crystallization, nor distillation, nor ordinary adsorption techniques are of value for the direct resolution of a pair of optical antipodes. For this purpose, use is made of special procedures which are collectively called the resolution of racemates.

Nearly all modern methods of resolution of racemates rely on the classical experiments carried out by Louis Pasteur about a hundred years ago. These experiments led to the following methods:

1. Mechanical separation, a method also known as spontaneous resolution. It depends on the crystallization of the two forms separately, which are then separated by hand.

2. Chemical resolution based on the formation of diastereomers.

3. Resolution by the biochemical method which makes use of the ability of microorganisms, their enzymic systems, to destroy one enantiomer more rapidly than the other.

4. Adsorption methods, in particular, chromatographic techniques.

The efficiency of the resolution of a racemate (racemic modification)

is estimated by the **optical purity** of the product obtained and is expressed by $p$ (in per cent):

$$p = 100 \frac{[\alpha] \text{ of product}}{[\alpha] \text{ of pure enantiomer}}$$

Numerically the optical purity corresponds to the excess of one antipode over the other in per cent: it *does not* coincide with the fraction of an optical antipode in the mixture. It is easy to see that each per cent of an impurity of the oppositely rotating optical antipode lowers the rotation of the mixture by 2 per cent. The percentage content of the impurity enantiomer is determined by the formula $(100-p)/2$, while the percentage content of the predominating enantiomer is evaluated through the use of the formula $(100 + p)/2$.

## 2.2. RESOLUTION OF RACEMATES BY MECHANICAL SEPARATION AND SPONTANEOUS CRYSTALLIZATION

In 1848 Pasteur obtained for the first time an optically active substance from an inactive one by **mechanical selection** of crystals. He observed that on crystallizing the sodium ammonium salt of racemic tartaric acid at a temperature below 27°C two types of crystals separated out from the aqueous solution, which were of two different forms and which were found to be related in shape as object to its mirror image (one the non-superimposable mirror image of the other). Having separated the two types of crystals with the aid of a magnifying glass and a pair of tweezers, Pasteur prepared aqueous solutions of each of the types and found that, in contrast to the original salt, these solutions were optically active: one type of crystal gave a levorotatory solution and the other, a dextrorotatory solution. This was the first experiment in the history of science that gave an optically active compound from an inactive one.

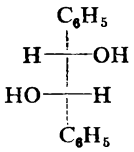
Young Pasteur realized the importance of his discovery and sent a letter about it to the notorious scientist Jean Baptiste Biot, who was well-known for his studies of optical activity. Not trusting the new facts completely, Biot wanted to check the Pasteur experiment. The narrative by Pasteur of this check-up has survived (5).

The simple experiment performed by Pasteur could not at first be reproduced until it was found out that the important factor was the temperature at which the crystallization took place: it is only at a temperature below 27°C that the conglomerate, i.e., a mixture of crystals of the levorotatory and dextrorotatory forms, separates out, while above this temperature the racemic compound crystallizes out, which cannot be separated mechanically. The equilibria of stereoisomeric forms became

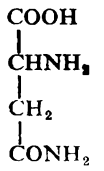
then the subject matter of fundamental studies by van't Hoff and his school. But in these works no preparative resolution was pursued, and examples of practical resolution by mechanical selection of crystals are but few in the history of science.

On gradual evaporation of the ethereal solution it is easy to obtain crystals of isohydrobenzoin I, up to 1 cm in size, and to separate them into the enantiomeric forms: in this way Erlenmeyer in 1897 succeeded in preparing optically active isohydrobenzoin with $[\alpha]_D = 7.3°$, which corresponds to less than 10 per cent of optical purity. It was only when ethyl acetate was used instead of the ether that Reed succeeded in preparing the optically pure crystals in 1927.

Closely related to the resolution by means of mechanical separation of crystals is **preferential crystallization,** which occurs, as it were, spontaneously. More often than not, this type of "spontaneous" isolation of one of the antipodes from a solution of a racemate can be effected by seeding the supersaturated aqueous solution of the racemate with a crystal of one enantiomer (inoculation). Not only a crystal of the enantiomer to be isolated but also an isomorphous crystal of a foreign substance may be used for seeding the solution. Thus, when a powder of crystals of glycocoll or glycine (a compound which is optically inactive and does not even contain an asymmetric atom) is used, optically active asparagine separates out from a supersaturated solution of racemic asparagine II:



I



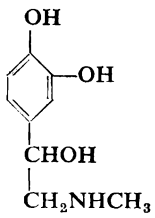
II

This case is, strictly speaking, a special version of **absolute asymmetric synthesis,** i.e., the preparation of an optically active compound without the participation of factors associated with living nature.

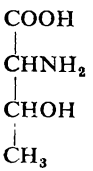
Neuberg in 1937 reported the isolation of optically active crystals from the potassium salt of 3-methylvaleric acid which was allowed to stand for a long time. The fractions obtained in these cases rotated the plane of polarized light only slightly, but in other cases a *complete resolution* by crystallization was reported. Thus, optically pure adrenaline III can be produced by reprecipitating (4 times) the hydrochloride of racemic adrenaline by pyridine from an aqueous solution. The method of preparing optically active threonine IV by means of spontaneous resolution of the racemate proved to be so effective that it was patented. From 20 kg of racemic 2,4-dioxo-3,3-diethyl-5-methylpiperidine V which was

subjected to 400 (!) crystallizations there was isolated 3 g of the optically pure dextrorotatory enantiomer. Spontaneous resolution by crystallization is also applicable to the base of chloramphenicol (VI), which is a valuable intermediate in the production of the antibiotic Chloromycetin (chloramphenicol).

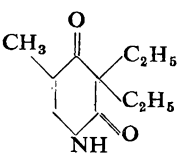
The reader is referred to the literature for additional material on the spontaneous resolution by crystallization (6).



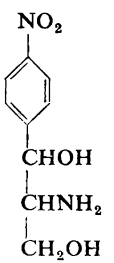
III



IV



V

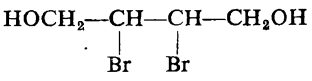


VI

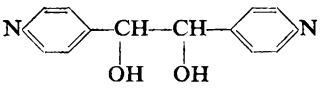
## 2.3. THE BEHAVIOUR OF ENANTIOMERS IN OPTICALLY ACTIVE SOLVENTS

Van't Hoff in his classical work (7) assumed that the solubilities of optical antipodes (enantiomers) in optically active solvents must be different. The possibility of using crystallization from an optically active solvent for the resolution of racemates was tested by a number of scientists at the turn of the century but no positive result was obtained, and so the resolution by this method was believed to be impossible. But in the thirties a successful resolution of racemates by crystallization from an optically active solvent was reported.

To account for the contradicting results it was assumed that the formation of spatially differing solvates (and, hence, those of different solubility) may occur only in those cases when the solute and solvent molecules interact at two points at least: for this to be achieved they must each have at least two polar groups. Guided by this working hypothesis, it became possible to resolve 2,3-dibromobutane-1,4-diol (VII) and 1,2-bis-(γ-pyridyl)-ethylene glycol VIII by crystallization from the diisopropyl ester of tartaric acid.



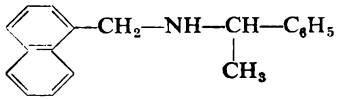
VII



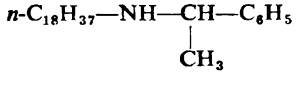
VIII

A similar result has been obtained by Dashkevich (8) who studied the interaction of mandelic acid with optically active solvents: the asymmetrizing effect of the solvent manifests itself only when hydrogen bonds are formed between the solvent and the compound to be resolved.

Another variant of the use of an optically active solvent is the distribution of the racemate to be resolved between the solvent and the optically inactive phase. Thus, 2,3-dibromobutane-1,4-diol was resolved by distribution between water and the esters of (+)-tartaric acid (9). Solutions of optically active secondary amines IX and X in chloroform have also been used as the optically active phase. By shaking them with an aqueous solution of the sodium salt of racemic mandelic acid or of racemic N-acetylalanine it is possible to obtain the last-named two compounds in optically active forms. It is curious and practically important that the amines IX and X used must not of necessity be 100% optically pure; this does not hinder the complete resolution of mandelic acid (10).



IX



X

## 2.4. RESOLUTION BY FORMATION OF DIASTEREOMERS

This method, which is the best of all the methods of resolution, consists in converting the enantiomers of a racemic modification into diastereomers: in certain cases only the biochemical method can compete with it. The principle underlying this method may be expressed by the following scheme:

$$(L_1 \times D_1) + D_2 \rightarrow \begin{cases} \rightarrow (L_1 \times D_2) \\ \rightarrow (D_1 \times D_2) \end{cases}$$

The racemic modification $(L_1 \times D_1)$ is treated with an optically active substance $D_2$ (a resolving agent): this results in the formation of a new pair of substances $(L_1 \times D_2)$ and $(D_1 \times D_2)$, which are no longer enantiomeric; they are diastereomers. We know that diastereomers differ in physical properties. The differences in solubility, vapour pressure, and adsorption coefficient are in many cases sufficient for the diastereomers to be separated by fractional crystallization, distillation or chromatography.

The resolution of racemates by means of diastereomer formation includes three successive operations: the formation of a pair of diastereomers, their separation, and the destruction of each of the diastereomers, this

resulting in the isolation of the enantiomers of the racemate being resolved. For all these stages to be successfully effected it is necessary that several conditions be fulfilled, which are defined at this point in the most general form.

It is obvious that the *formation of diastereomers* is possible only if the compound to be resolved has a chemically active group capable of interacting with a suitable asymmetric reagent (resolving agent). Generally speaking, the nature of this group is immaterial. It is only essential that the bonds of the asymmetric centre remain intact during the reaction and the formation and separation of diastereomers occur easily so that the possibility of racemization is reduced to a minimum. In practice, *diastereomeric salts* are most often formed, all other reactions being of incomparably less importance. The chemical nature of the asymmetric reagent must correspond to the nature of the compound to be resolved. Thus, racemic acids may be separated by optically active bases. On the other hand, a basic racemate may be resolved by using an optically active acid.

Most asymmetric reagents are rather expensive and therefore the possibility of regenerating a reagent after the resolution is complete is important for practical estimation of the suitability of the method of resolution used (especially for production purposes). Perhaps, the only reagent that poses no problem of regeneration because of its low cost is tartaric acid.

The most important problem is the selection of an asymmetric reagent: the diastereomers formed with its participation must differ as strongly as possible in solubility (or in other properties if methods other than crystallization are employed for the purpose). Unfortunately, no theoretical principles or at least empirical rules have so far been worked out for the selection of asymmetric reagents. In practical work, the researcher has nothing else to do but to simply test all the available reagents until a suitable one is found.

The solvent used is also important: the success of a resolution depends on the solvent to no lesser an extent. The solvent has also to be selected empirically; use is most frequently made of water, alcohols, acetone, ethyl acetate. In some cases, it is very difficult to find a good solvent, and the diastereomers have to be separated by several fractional recrystallizations.

The purity of the diastereomeric salt obtained is usually established by the constancy of its melting point and rotation after further crystallizations. This criterion may however be unreliable: it was reported in the literature (11) that the diastereomeric salt of β-ethoxy-β-phenylethylamine with (+)-camphorsulphonic acid was brought to constant rotation and the salt was then decomposed to give an amine with a rotation of $[\alpha]_D = -4.3°$, while the optically pure amine produced in a

different way had a specific rotation of $[\alpha]_D = -104.2°$. Such cases are accounted for by the formation of "partial racemates", the composition of which remains unchanged upon further crystallizations, even though they consist of mixtures of the two diastereomeric salts in a constant proportion. In principle, this phenomenon is analogous to the formation of constantly boiling (azeotropic) mixtures of liquid substances which cannot be separated by distillation.

The temperature may also play an essential role in the process of resolution.

Cases are not rare where only partial resolution is accomplished through diastereomer formation. In such cases, additional purification is required, which can be effected either by recrystallization of the isolated impure enantiomer from a suitable solvent (12) or by the formation of complexes (13).

As has already been pointed out, when racemates are resolved by means of diastereomer formation, use is made of auxiliary optically active substances — asymmetric reagents (resolving agents), whose nature is dependent on the nature of the racemate to be resolved. As a concrete example, let us consider the resolution of racemic hydratropic acid by means of optically active (—)-α-phenylethylamine [also called (—)-α-phenethylamine]. The interaction of the two compounds gives a pair of diastereomeric salts (14):

$$\begin{matrix}(+)\text{-}C_6H_5—CHCH_3—COOH \\ (-)\text{-}C_6H_5—CHCH_3—COOH\end{matrix} + (-)\text{-}C_6H_5—CHCH_3—NH_2 \longrightarrow$$

$$\longrightarrow \begin{matrix}C_6H_5—\overset{(+)}{C}HCH_3—COOH\cdot H_2N—\overset{(-)}{C}HCH_3—C_6H_5 \\ C_6H_5—\overset{(-)}{C}HCH_3—COOH\cdot H_2N—\overset{(-)}{C}HCH_3—C_6H_5\end{matrix}$$

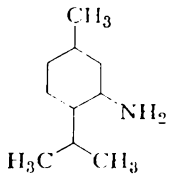
The salt of the (—)-acid is less soluble: it separates out from solution and is purified by 4 recrystallizations from water. The pure diastereomeric salt of the (—)-acid with a (—)-amine is decomposed by hydrochloric acid, and the separated (—)-hydratropic acid is extracted by ether and distilled; it has a $[\alpha]_D$ value of —120° (in benzene solution), and the yield is about 10 per cent of the total amount of the racemic acid taken. The asymmetric reagent [(—)-α-phenylethylamine] remains in the form of a hydrochloride in aqueous solution: it can easily be recovered.

As a result of the process described, there occurred, so to speak, a "reproduction of optical activity" — the active compound (amine) used for the resolution was retained and, besides, a new optically active compound, (—)-hydratropic acid, was formed. Other resolutions are effected in an analogous manner: the difference is in the asymmetric reagents and solvents used, the number of recrystallizations required,

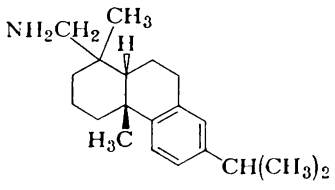
and in the details of the resolution of an optically active compound and the regeneration of the resolving agent.

Note that the method just described leads to the formation of only one enantiomer of hydratropic acid. The second (more-soluble) diastereomer left in the mother solution is invariably contaminated with the first isomer and so the second enantiomer cannot be obtained in a pure state; for this purpose, use is made of another antipode of the asymmetric reagent, (+)-α-phenylethylamine. This is one of the advantages of the use of synthetic asymmetric reagents which are, as a rule, available in both enantiomeric forms, whereas natural compounds (say, alkaloids) are available only in one of the enantiomeric forms. The book "Foundations of Stereochemistry" written by Terentiev and Potapov (5) contains numerous examples of resolution of acids, amines, and other compounds. Some new examples are additionally presented in Table 2.1, which refer to the resolution of carboxylic acids into optical antipodes.

The number of basic asymmetric reagents suitable for the resolution of acids is rather great: apart from the many alkaloids (use is most frequently made of quinine, cinchonine, brucine, strychnine), synthetic compounds are also extensively used, such as α-phenylethylamine, α-benzylethylamine, α-(naphthyl-1)-ethylamine, the base of chloramphenicol, $C_9H_{12}O_4N_2$, menthylamine XI, dehydroabietylamine XII.




XI




XII

The second route for preparation of optically active acids is by the resolution of racemates via diastereomeric esters. Thus, for example, phenylchloroacetic, α-phenylhydrocinnamic, and β-methylhydrocinnamic acids have been resolved via esters with (—)-menthol. Diastereomeric esters are separated in such cases by crystallization. Since esters (unlike salts) are volatile compounds, diastereomeric esters must in principle have different boiling points, and distillation may be used for their separation. But, as a matter of fact, the difference between their boiling points is so small that only partial resolution can be achieved even by distillation carried out on highly effective columns. For example, the distillation of the ester formed by racemic 2-methylbutyric acid and (+)-2-methyl-1-butanol in vacuum on a column with an effectiveness of 60 theoretical plates gave fractions whose specific rotation varied from +2.0° to +3.3°. The 2-methylbutyric acid isolated from the head and tail fractions had

TABLE 2.1. EXAMPLES OF RESOLUTION OF RACEMATES OF CARBOXYLIC ACIDS INTO OPTICAL ANTIPODES

| Acid to be resolved | Resolving agent | Solvent | Reference |
|---|---|---|---|
| 2-(Carboxymethylmercapto)-propionic acid | Ephedrine | Ethanol | (15) |
| 2-(Isopropylideneaminohydroxy)-propionic acid | Ephedrine | Ethanol | (16) |
| 2-Phthalimidobutyric acid | Ephedrine | Ethanol | (17) |
| 2,3-Dimercaptosuccinic acid | Brucine | Acetone | (20) |
| 2-Methylsuccinic acid | Strychnine | Ethanol | (18), (19) |
| 2-Hydroxyundec-10-enic acid | α-Phenylethylamine | Diethyl ether | (21) |
| Cyclohexene-3-carboxylic acid | Quinine | Acetone | (22) |
| Hydrindanecarboxylic acid | Brucine | Acetone + water | (23) |
| 2-Mercaptophenylacetic acid | Cinchonidine | Acetone | (24) |
| *trans*-3-Phenylglycidic acid | α-Phenylethylamine | Ethanol | (25) |
| 2-Phenylalkanic acids | α-Phenylethylamine | Ethanol | (26) |
| Dichlorophenylsulphinyl-acetic acids | Brucine, strychnine, cinchonidine | Ethanol | (27) |
| 2-(*p*-Hydroxyphenyl)-succinic acid | Brucine | Ethanol | (28) |
| 3- and 4-*tert*-Butylphenoxypropionic acids | Brucine, strychnine | Dil. ethanol | (29), (30) |
| 2-(Chloronitrophenoxy)-propionic acids | Cinchonine | Ethanol | (31) |
| 2-Arylhydroxypropionic acids | α-Phenylethylamine, strychnine | Ethanol | (32) |
| α-(4-Bromonaphthyl-1)-propionic acid | Brucine, cinchonidine | Acetone | (33) |
| Acenaphthene-1-carboxylic acid | Cinchonine | Methanol | (34) |

a specific rotation of —0.25° and +0.29°, respectively (the optical purity was about 1.5 per cent) (35). The diastereomeric esters of (—)-menthol with 2-methylbutyric or 2-methoxypropionic acid have also been partially separated by distillation.

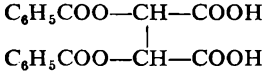
The chemical nature of the carboxyl group can be modified so as to make possible the formation of diastereomeric salts with optically active acids as well; this has been demonstrated by the example of the amidines of substituted mandelic acids, which have been resolved into optical antipodes via diastereomeric salts with optically active mandelic acid (36).

The alkaloids and other optically active bases are also applicable for preparing optically active sulphonic acids (37).

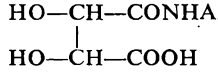
For racemic amines to be resolved, optically active acidic resolving agents are required. The number of such resolving agents is not great

as compared with those used for the resolution of racemic acids (by means of alkaloids and synthetic bases). The acidic reagent most frequently used is (+)-tartaric acid. A typical example of its use is the preparation of optically active α-phenylethylamine. If a racemic amine is mixed with (+)-tartaric acid in a warm methanol solution, an almost pure diastereomeric salt containing a (—)-amine will separate out (38). But if water is used instead of methanol as the solvent, the amine obtained will be only slightly optically pure. This is a spectacular example of the strong influence of the solvent on the results of resolution.

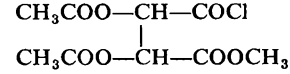
Other acidic resolving agents have been produced on the basis of the readily available (+)-tartaric acid: dibenzoyltartaric acid XIII, tartranilic acids XIV (39), the acid chloride of monomethyl ester of diacetyltartaric acid (methyl diacetyltartrate), XV (40).



XIII



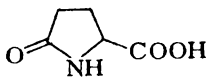
XIV



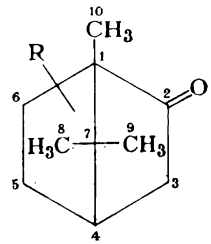
XV

Tartaric acid is probably the only resolving agent, the availability and low cost of which excludes the necessity of regeneration.

A rather available acidic resolving agent is pyroglutamic acid XVI, which is easily prepared when natural glutamic acid is heated. Other natural, optically active acids, such as mandelic, malic, and camphoric acids, are less readily available. Since the number of natural acidic resolving agents is very limited, many *synthetic* reagents of this type have been produced not only by the above-mentioned modification of (+)-tartaric acid but also on the basis of other optically active substances.



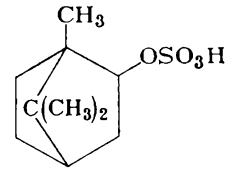
XVI



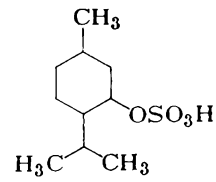
XVII R= 10-$SO_3H$

XVIII R= 3-$SO_3H$

XIX R= 9-$SO_3H$



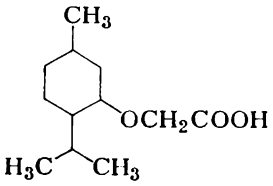
XX



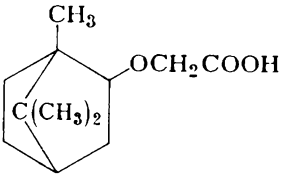
XXI

A large group of resolving agents of acidic character have been prepared from terpene ketones and alcohols by way of their conversion into sulphonic acids or acid sulphates. The most important of these are the following: α-, β-, and π-camphorsulphonic acids XVII-XIX, bornylsulphuric acid XX, menthylsulphuric acid XXI. The last two compounds are easily prepared by the action of dioxanesulphotrioxide on the corresponding optically active alcohols (borneol and menthol). They have been used for the resolution of racemic α-phenylethylamine and its analogues (41).

Optically active alcohols are converted into acidic asymmetric reagents also by the action of chloroacetic acid on the corresponding alkoxides. In this way there have been prepared, for example, menthylhydroxyacetic acid XXII and bornylhydroxyacetic acid XXIII.



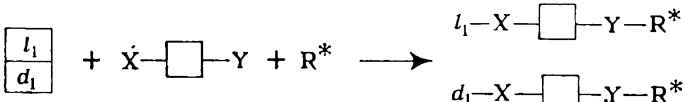

XXII




XXIII

The acidity of such compounds is lower than that of sulphonic acids or acid sulphates, and therefore their salts with weak organic bases are less stable.

In synthetic acidic asymmetric reagents, the sulphuric- or hydroxyacetic-acid residue plays the role of a "handle" whose bifunctional character enables the union of the resolving agent proper (a terpene ketone or alcohol) and the compound to be resolved into a single molecule. Generally speaking, any bifunctional compound (or group) capable of uniting with the compound to be resolved via one of the functions and with the asymmetric reagent R* through the other may be employed as the "handle". This may be illustrated by the following scheme:



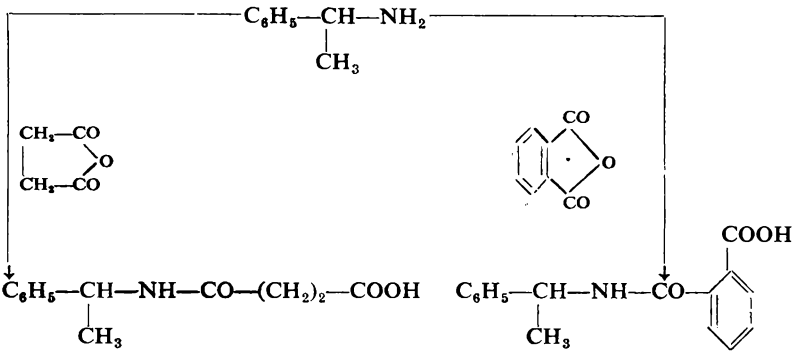

Racemate to be resolved

"Handle"

Pair of diastereomers

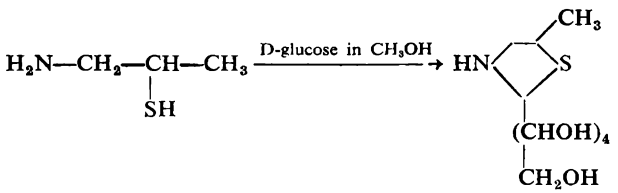
The use of acidic "handles" permits a large number of diversified versions of resolution to be developed even with one optically active substance. Thus, an amine, for instance, can be converted into an acidic

resolving agent. This has been shown by the conversion of optically active α-phenylethylamine into an acid amide through the action of succinic or phthalic anhydride (42):

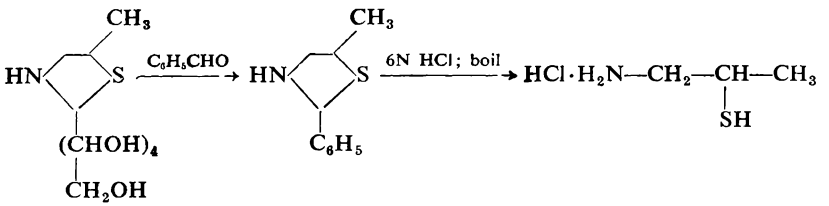


The reagents obtained in this way have been successfully used for resolving α-phenylethylamine itself, α-benzylethylamine, 2-amino-1-butanol, and the base of chloramphenicol.

To resolve a compound containing two functional groups — the amino and the thiol group, the conversion into a cyclic product by the action of D-glucose has been used:



The diastereomers obtained were separated by crystallization, after which the glucose was removed by an exchange reaction with benzaldehyde and then optically active aminothiol was isolated by hydrolysis (43):

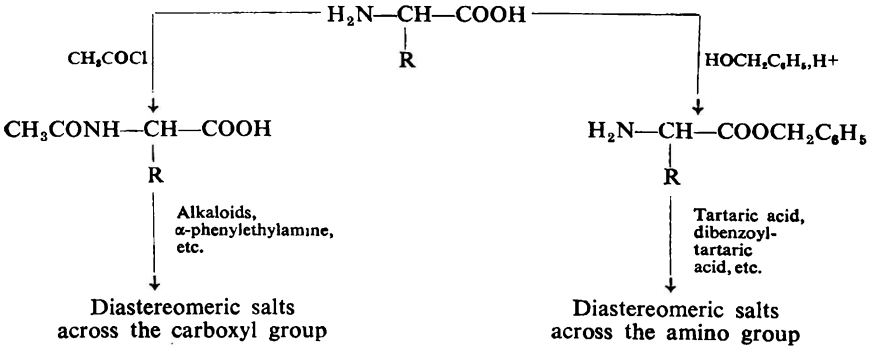


Some examples of resolution of amines and other bases are listed in Table 2.2.

TABLE 2.2. EXAMPLES OF RESOLUTION OF RACEMIC ORGANIC BASES INTO ENANTIOMERS

| Substance to be resolved | Resolving agent | Solvent | Reference |
|---|---|---|---|
| 3-Methyl-3-hexylamine | Tartaric acid | Water | (44) |
| Aminoolefins of the general formula $CH_2{=}CH(CH_2)_m\,\underset{\displaystyle CH_3}{\underset{\vert}{CH}}(CH_2)_n\,NRR'$, where $m$ and $n = 0$ or 1; R, R′ = H, *iso*-$C_3H_7$, *iso*-$C_4H_9$ | Tartaric acid | Ethanol | (45) |
| Benzylethylamine | Tartaric acid | Ethanol | (46) |
| 1,3-Diphenylpropylamine | Tartaric acid | Ethanol | (47) |
| 2-Aminopropionitrile | Tartaric acid | Ethanol | (48) |
| α-Aminophenylacetonitrile | Tartaric acid | Methanol | (48) |
| α-Dimethylamino-α-methylpropiophenone | Dibenzoyltartaric acid | Acetone | (49) |
| Alkylphenylpyridylcarbinols | Tartaric acid, camphor-10-sulphonic acid | Ethanol | (50) |
| Pyridylethylamines | Tartaric acid | Ethanol | (51) |
| *trans*-2,6-Dimethylpiperidine | Mandelic acid | Methanol + diethyl ether | (52) |
| Methylphenylsulphoximine | Camphor-10-sulphonic acid | Acetone | (53) |

Racemic *amino acids* can be resolved by using salt formation across the carboxyl group (after the amino group is protected) and also by salt formation across the amino group (after the carboxyl group is converted, for example, into the ester group):



The resolution of racemic amino acids into their enantiomers via their N-acyl derivatives was first used by Emil Fischer in his classical works. As early as the end of last century he obtained L-alanine in this way, and later many other optically active amino acids contained in proteins. Fischer especially frequently used the benzoyl or formyl protection of the amino group. Many of the resolutions of amino acids have, however, been effected through the use of other protecting groups — the acetyl, *p*-nitrobenzoyl, tosyl, and other groups. Thus, for example, the tosyl protection has been employed for the resolution of serine; the phthalyl group for the resolution of α-aminobutyric acid with ephedrine as an optically active base; *p*-nitrophenylsulphenyl protection for the resolution of phenylglycine, phenylalanine, proline with ephedrine, pseudoephedrine or the base of chloramphenicol as optically active bases. The carbobenzoxy protection has also been found to be useful for the resolution of many racemic amino acids.

Another method, the esterification of the carboxyl group and the preparation of a salt with an optically active acid, has been employed much less frequently for the resolution of racemic amino acids into their antipodes. Fischer made an attempt to resolve α-aminocaproic acid by this method, but he was not fully successful. Probably, his remark that although the method is in principle applicable its use is complicated by the easy saponification of esters held up researchers from further work in this direction. Beginning from 1957 there appeared the works of Losse who successfully resolved many racemic α-amino acids by using isobutyl or benzyl alcohol for the esterification and dibenzoyltartaric acid as the asymmetric reagent.

A further version of the resolution of amino acids has been described, namely, their conversion into diastereomeric esters with (—)-menthol (54).

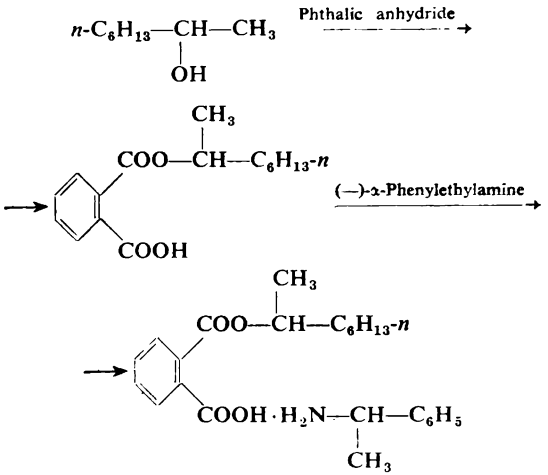
Amino acids can also be prepared in an optically active form via the corresponding aminonitriles with subsequent hydrolysis: having no acid function, aminonitriles normally form diastereomeric salts with acidic resolving agents. In this way, α-aminophenylacetic acid has been obtained via the salt of α-aminophenylacetonitrile with (+)-tartaric acid (55).

*Alcohols* can be directly transformed into diastereomeric esters by reaction with optically active acids. More often than not, diastereomeric esters are prepared by using menthylhydroxyacetic acid XXII and bornylhydroxyacetic acid XXIII (56).

The fluorinated alcohols $CF_3$—CH(OH)—R (R=$C_4H_9$, $C_6H_5$) have been resolved via acid esters with 3β-acetoxy-$\Delta^5$-etienic acid (57), and steroidal alcohols via derivatives of diacetyltartaric acid.

But the method of resolution via diastereomeric esters has not gained wide recognition because well-crystallizing substances can be obtained in rare cases. Another version of the method is employed more frequently: the alcohol to be resolved is first converted into an acid ester of a dicarboxylic acid, which is capable of forming salts with an optically active

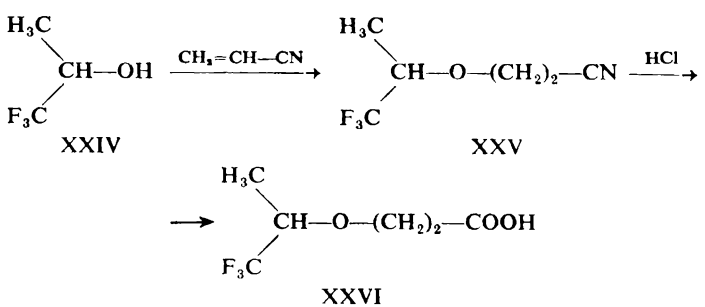
base. An example is the resolution of 2-octanol via the salt of its acid phthalate with α-phenylethylamine (58):




The less soluble diastereomer formed by the phthalate of (+)-2-octanol and (—)-α-phenylethylamine separates out from the acetone solution and is additionally purified by 1 or 2 crystallizations from the same solvent. This diastereomer is then treated with soda to convert the phthalate into the sodium salt and to regenerate (—)-α-phenylethylamine. The optically active 2-octanol is isolated by acid hydrolysis; the resulting alcohol can be conveniently distilled with steam.

The "handle" which imparts acidic properties to the substance can add by means of an ether linkage as shown for the resolution of triarylcarbinols via compounds of the general formula $Ar_3C—O—CH_2COOH$ (59).

The conversion of alcohol XXIV (via the ester derivative XXV) into an acidic compound has also been used to resolve racemic 1-trifluoromethylethanol (60):



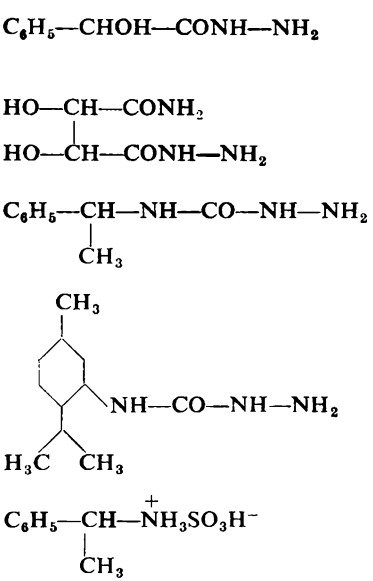

XXIV XXV XXVI

Compound XXVI was transformed into a salt with quinine, the diastereomers were separated, and acid hydrolysis was carried out, as a result of which an optically active alcohol with $[\alpha]_D^{25} = +2.63°$ was obtained.

Inositols have been resolved by their conversion first into acid oxalates by the action of oxalyl chloride and then into diastereomeric salts with quinidine or (—)-α-phenylethylamine (61).

There have been published many reviews devoted to methods of resolution of alcohols into their optical antipodes (56, 62).

Optically active *aldehydes* and *ketones* are prepared through the use of reagents for the carbonyl group, an optically active radical being preliminarily introduced into these reagents; for example:



$C_6H_5$—CHOH—CONH—$NH_2$ — Hydrazide of (+)-mandelic acid; used for resolution of benzoin.

HO—CH—$CONH_2$
HO—CH—CONH—$NH_2$ — Amidohydrazide of (+)-tartaric acid; used for preparing optically active 2-phenylcyclopentanone.

$C_6H_5$—CH(—$CH_3$)—NH—CO—NH—$NH_2$ — (−)-α-Phenylethylsemicarbazide; used for resolution of benzoin.

$CH_3$, NH—CO—NH—$NH_2$, $H_3C$, $CH_3$ — Menthylsemicarbazide; used for resolution of benzoin.

$C_6H_5$—CH(—$CH_3$)—$\overset{+}{N}H_3SO_3H^-$ — Acid sulphite of (+)-α-phenylethylamine; used for preparing optically active 3-methylcyclohexanone.

Optically active hydrazones, hydrazides, and semicarbazides have been obtained from other compounds as well (63). The possibility of their use for resolution has been largely tested by using the same compounds: benzoin, hydratropaldehyde and 3-methylcyclohexanone.

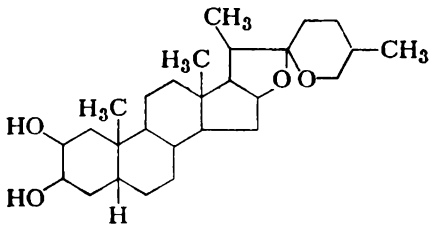
## 2.5. RESOLUTION VIA MOLECULAR COMPOUNDS

The method of resolution via molecular compounds is closely related to resolution by means of diastereomer formation. In both cases, the racemate is converted into a pair of diastereomers, the only difference being

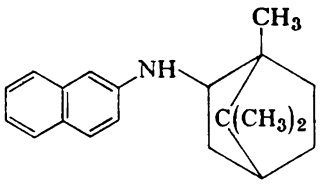
that resolution via diastereomers involves the formation of stable chemical compounds, whereas resolution via molecular complexes gives readily decomposable molecular compounds only. Theoretically, the latter method of resolution has an advantage over resolution by conversion to diastereomers: both the preparation and decomposition of molecular compounds occur under mild conditions which reduce the possibility of racemization to a minimum.

The first observations in this respect were made by Pasteur. He observed that the amide of (—)-malic acid forms molecular compounds of different properties with the enantiomeric amides of tartaric acid: with the amide of (+)-tartaric acid there are formed large transparent crystals, whose solubility in water at 20°C is 18 per cent; with the amide of (—)-tartaric acid, thin silky needles are formed, whose solubility is almost two times higher. Free malic and tartaric acids also form diastereomeric molecular compounds, a fact that may be used for resolution.

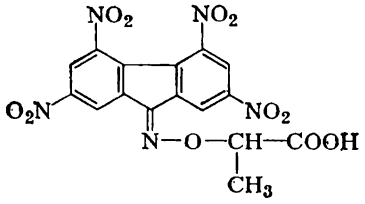
Digitonin XXVII has been used as a complex-former to resolve racemic α-terpineol, tetrahydro-β-naphthol, and isocarvomenthol. Racemic *sec*-butylpicramide has been resolved via a complex with (±)-β-naphthylcamphylamine XXVIII.



XXVII



XXVIII



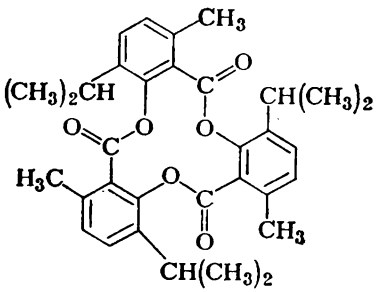
XXIX

Aromatic hydrocarbons and esters can be resolved into optical antipodes via molecular complexes with optically active nitro compounds. For example, (—)-α-(2,4,5,7-tetranitrofluorenylidene-9-aminohydroxy)-

propionic acid XXIX has been used for preparing an optically active hydrocarbon of the paracyclophane series (64).

It has proved possible to effect stereospecific exchanges of ligands in copper complexes of amino acids. Thus, if a copper complex of L-alanine is mixed with racemic aspartic acid, there will be formed a copper complex of D-aspartic acid (65).

Of special interest are experiments involving the resolution of racemates via complexes with optically inactive compounds. Here two different mechanisms are possible. In some cases, the formation of a molecular compound weakens the van der Waals forces that unite the molecules of the enantiomers into a racemate particle; conditions are thus developed for a particularly facile "spontaneous resolution" upon crystallization. An example is tri-*o*-thymotide XXX, a compound with molecular chirality.



XXX

Trithymotide is capable of giving molecular compounds with hexane, benzene, and chloroform. The crystals that separate out are indistinguishable from one another in external appearance, but if a single crystal is dissolved in chloroform, it will turn out that both levo- and dextrorotatory crystals are present; spontaneous racemization takes place rapidly in solution. If such a molecular compound is obtained in the presence of a third substance, which is in its turn a racemate, then only one of the enantiomers of this substance will predominantly crystallize out. This type of effect has been observed, for example, in the trithymotide-chloroform-*sec*-butyl bromide system.

Similar phenomena have been detected by Schlenk (66) during his study of "inclusion compounds" formed by urea. Inclusion compounds are known to be formed as the result of the second component fitting into the holes (channels) formed in urea crystals. Urea is a symmetrical substance, but upon crystallization it forms a hexagonal screw lattice

which may be right- or left-handed. If the substance contained in an inclusion compound is a racemate, then favourable conditions obtain for the formation of diastereomeric inclusion compounds; for example:

(1) The right-handed lattice of urea · (+)-2-chlorooctane.

(2) The right-handed lattice of urea · (—)-2-chlorooctane.

Like any other pair of diastereomers, these diastereomers too differ sufficiently in physical properties to allow separation to be made.

Inclusion compounds also form optically active substances. The cyclodextrins formed by them have also been employed for resolution.

Inclusion compounds are particularly important for the preparation of optically active forms of substances that contain no functional groups suitable for the formation of diastereomers: therefore, apart from halogen derivatives, this method is promising for the preparation of optically active hydrocarbons too. Optically active 3-methyloctane and 3-methylnonane have been prepared via inclusion compounds with urea (67).

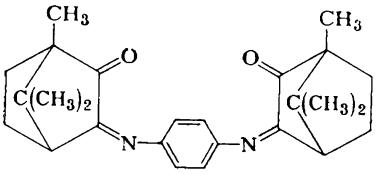
## 2.6. RESOLUTION BY ADSORPTION METHODS

By taking advantage of the different adsorption coefficients of diastereomers, it is possible to separate them by chromatography through the use of ordinary adsorbents. Thus, the ester of 2-butanol and (—)-mandelic acid is separated into two diastereomers chromatographically on a column filled with Dowex-50W-X2 (68). The diastereomeric N-(1-phenylethyl)-urethanes of 1-octen-3-ol, 2-octanol, and other alcohols are separated by thin-layer chromatography on silica gel (69).

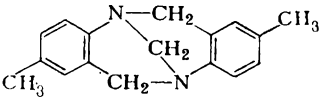
The use of chromatographic method instead of crystallization is convenient and useful in a number of cases, but, in principle, nothing new is introduced by this variant of resolution by adsorption separation. More interesting is another version which brings about a direct separation of enantiomers on an optically active adsorbent.

Quartz which is able to form chiral crystals exhibits different adsorptive power for optical antipodes; a number of inorganic complex compounds have been prepared in an optically active form by this method, but attempts to resolve 2-butanol and other organic compounds have failed (70).

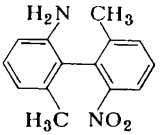
A sufficiently good asymmetric adsorbent is lactose, which has been used in the resolution by chromatography of *p*-phenylene-bis-(iminocamphor) XXXI, Tröger's base XXXII (a compound with an asymmetric nitrogen atom), chloramphenicol, and 2-amino-2′-nitro-6,6′-ditolyl XXXIII.



XXXI



XXXII



XXXIII

Brucine may also be used as an adsorbent, as has been demonstrated by the example of resolution of the acid phthalate of 2-octanol. Starch has also been employed successfully as an optically active adsorbent (71).

In all the cases mentioned above, use has been made of natural optically active adsorbents. Synthetic polymers with an optically active residue introduced into them have also been tried for the purpose. The various optically active substances are now prepared successfully by using synthetic optically active adsorbents. For example, racemic mandelic acid has been resolved on a polyacrylic polymer containing quinine residues as optically active components. A number of authors have employed polymers from chloromethylated polystyrene and divinylbenzene, residues of optically active α-phenylethylamine being preliminarily introduced into the polymer (due to the reaction with chlorine). Amino-acid residues have also been introduced into polymers as optically active components. In all experiments in which such optically active synthetic adsorbents were used, only a partial resolution was achieved (the optical purity was only a few per cent). It has been calculated that a column 2.3 km long (!) would be required for a complete resolution to be accomplished.

Particularly interesting in comparison with these partly successful results is the adsorption method of resolution developed by Rogozhin, Davankov and coworkers (72). Residues of an optically active amino acid are introduced into a polymeric solid adsorbent. A solution of the salts of copper or any other complex-forming metal is passed through a column filled with the adsorbent; the metal forms a complex with the amino acid fixed in the support. A solution of a racemic amino acid $L_1D_1$ is passed through the thus prepared column. Two diastereomeric

complexes may be formed due to the complex formation with the participation of the cupric ion and the optically active amino acid $L_2$:

| | |
|---|---|
| $L_2$—Cu(II)—$L_1$ | (a complex consisting of similar components) |
| $L_2$—Cu(II)—$D_1$ | (a complex consisting of dissimilar components) |

In a number of cases, the stabilities of such complexes are substantially different, and therefore one of the enantiomers of the amino acid to be resolved passes through the column faster than the other, which enables a chromatographic separation to be effected.

Polystyrene partly cross-linked by biphenyl bridges may be employed as the support. When this polymer was chloromethylated and then treated with L-histidine, it was possible to obtain proline 94 per cent optically pure in the presence of salts of divalent copper, and aspartic acid with an optical purity of 35 per cent. The best result has been obtained on a chloromethylated styrene-divinylbenzene copolymer carrying L-proline; by passing first the cupric salts and then racemic proline through such a column it is possible to resolve the racemic proline with 100 per cent yield and 100 per cent optical purity.

Gas-liquid chromatography (GLC) is also employed to resolve racemates. For example, the following procedure has been suggested: racemic α-amino acids are converted into esters with optically active alcohols, the trifluoroacetyl residue is added to nitrogen to improve the volatility and the diastereomers obtained are separated by means of preparative gas-liquid chromatography (121). A number of amino acids have been resolved in this way via their (—)-2-butanol esters and trifluoroacetyl derivatives. The trifluoroacetyl derivatives of optically active amino acids have in their turn been employed for the gas-chromatographic resolution of racemic alcohols via the corresponding esters. In the case of 3,3-dimethyl-2-butanol, 98 per cent optical purity has been attained (73).

Using optically active liquid phases, it is possible to directly separate optical antipodes; this has been demonstrated for the *tert*-butyl ester of N-trifluoroacetylalanine which was resolved by means of gas-liquid chromatography on a column filled with chromosorb impregnated with the cyclohexyl ester of N-trifluoroacetyl-L-valyl-L-valine (74).

Paper chromatography too has been employed for resolution of racemic modifications: the paper was impregnated with a solution of (+)-camphorsulphonic acid, or else unimpregnated paper was used (since paper itself is optically active).

It is especially interesting that ordinary adsorbents can be made stereoselective by special treatment with optically active substances which are then completely removed. For example, silica gel was prepared for this

purpose by acidifying a solution of sodium silicate which contained an optically active substance—camphorsulphonic acid or mandelic acid. The resulting gel also captured a part of the optically active substance from solution; the gel was dried and purified by washing it off from the optically active substance, and a stereoselective sorbent was prepared, which exhibited higher adsorptive power for the optical antipode that was present in the solution during the preparation. When the racemate was passed through such a sorbent, there was observed a preferential adsorption of that enantiomer, the "memory" of which had been retained on the sorbent (75). If alumina is treated in an analogous way, the properties of a stereoselective sorbent can be imparted to it as well (76).

Additional material on the chromatographic separation of racemates and stereoisomeric compounds in general can be found in the literature (77).

* * *

Concluding the consideration of methods of resolution of racemic modifications, mention should be made of some methods that have been tested in isolated cases or have been assessed for applicability only theoretically or else have not been tested at all. Thus, there are data indicating that the surface tension on the interface with an optically active liquid is different for (+)- and (—)-forms. Therefore, if a liquid racemate is emulsified in an optically active liquid, the enantiomers may be expected to precipitate with different velocities (78).

The distribution of the brucine salts of racemic acids between water and chloroform has been described (79). Since highly efficient apparatuses have been designed for countercurrent extraction, this method may be very promising; several experiments of this kind have been reported in the literature (80). The separation of diastereomeric salts by taking advantage of their different densities and rates of diffusion in an optically active medium has been suggested.

Numerous reviews have been devoted to methods of resolution of racemates; the reader is referred to the latest reviews (81).

## 2.7. BIOCHEMICAL PREPARATION OF OPTICALLY ACTIVE COMPOUNDS

The importance of steric factors in biochemical processes was first noted by Pasteur when in 1857 he observed the preferential destruction by some microbes (e.g., by the mould fungus *Penicillium glaucum)* of the dextrorotatory form of tartaric acid. But if the racemate was allowed to be attacked by the mould, the levorotatory enantiomer was left intact

so that an excess of it could be accumulated in the solution and obtained in a pure state. This observation gave rise to the biochemical method of resolution of racemates — the third method of Pasteur.

The biochemical method is especially successfully used in a number of variants for preparing optically active amino acids. Thus, in the fermentation process yeasts react preferentially with the L-forms of amino acids, leaving the D-antipodes untouched, which accumulate and can be isolated in a pure state. This method has also been used to prepare optically active D-amino acids from racemic amino acids by the action of growing cultures of *Penicillium glaucum*, *Aspergillus niger*. The enzyme lipase extracted from the hog liver exhibits stereospecificity in the hydrolysis of esters of mandelic acid and related compounds. Phosphatase has the same effect on the phosphate esters of terpene alcohols. Numerous enzymatic resolutions of racemates of amino acids have been accomplished by using the action of the enzyme papain.

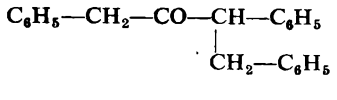
The most important for the biochemical preparation of amino acids is the method of stereospecific hydrolysis of esters of amino acids and of their N-acyl derivatives. Under the action of the enzyme acylase, N-acetyl-L-methionine is hydrolysed, say, 1000 times faster than the acetyl derivative of D-methionine. The analogous effect is exerted by acylase on other N-acyl derivatives of amino acids, the degree of stereospecificity depending on the nature of both the amino acid itself and the N-acyl residue (82). The results obtained with acylase on a cellulose support are interesting (83).

## 2.8. RACEMIZATION

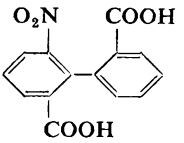
Many optically active substances become more and more inactive with time until their optical activity completely disappears, a process known as **racemization.** It is important to note that racemization is not accompanied by the breakdown of a substance in the chemical sense: the composition, structure, and chemical properties of the substance are retained, and only optical activity is lost.

Optical activity may disappear simply after a more or less prolonged storage of an optically active substance, the process being described as **autoracemization.** Autoracemization can be observed with substances in the solid and liquid states and in solutions. An example of the autoracemization of a solid substance is the complete loss of optical activity by (+)-phenylbromoacetic acid after three years of its storage, a fact observed by Walden. The analogous behaviour is shown by a related liquid substance—the ethyl ester of bromosuccinic acid (in general, autoracemization is most often displayed by optically active substances that have a halogen atom attached to the chiral centre).

Much more frequently racemization takes place not spontaneously but under the influence of some physico-chemical factors. Alkaline agents are often the catalysts for racemization; an important practical conclusion follows from this — when working with optically active compounds one must avoid using alkaline media if possible. Racemization, however, can also be catalysed by protons; for example, the dextrorotatory 1,3,4-triphenyl-2-butanone XXXIV racemises readily in the presence of concentrated sulphuric acid at room temperature.



XXXIV



XXXV

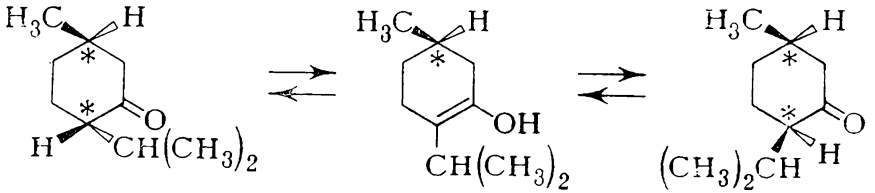
The catalysts used for the racemization of α-halogen-substituted acids and their esters are halide ions. Apparently, many of the processes that were formerly regarded as cases of autoracemization are actually induced by traces of catalysts. It has been shown, for example, that the autoracemization of the ester of bromosuccinic acid can be stopped if metallic silver is added to it, which binds the traces of bromide ions. Evidently, even the negligible alkalinity that appears in the leaching of glass may also catalyse racemization: for example, a solution of (+)-mononitrodiphenic acid XXXV in cyclohexanone racemises in a glass vessel about 60 times faster than in a quartz one.

The rate of racemization is considerably influenced by the solvent used. For instance, an aqueous solution of potassium hydroxide saponifies the ethyl ester of (—)-mandelic acid with retention of optical activity, but when an alcoholic solution of alkali is used for the saponification, the acid formed is completely racemized.

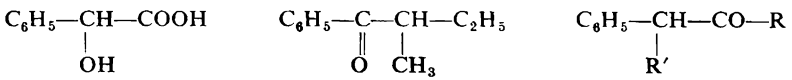
Substances may differ significantly in their optical stability. For example, lactic and mandelic acids and alanine undergo racemization readily. Less easily racemizable are, for instance, amyl alcohol and α-phenylethylamine. The diisobutyl ester of tartaric acid is difficultly racemizable: it does not lose optical activity when heated for many days at a temperature of up to 200°C. Compounds that practically do not undergo racemization are hydrocarbons with a tertiary asymmetric carbon atom, say, *sec*-butylbenzene, $C_6H_5—CH(CH_3)—C_2H_5$. It is easy to see even from the examples given above that substances which are slightly chemically active are in general less prone to racemization.

A number of hypotheses have been put forward to account for racemization. One of the most widespread is the hypothesis of the enolization mechanism of racemization advanced by Beckmann in the last century.

It is based on experimental data indicating that racemization takes place especially easily if there is a carbonyl group next to the chiral centre. For example, when menthone undergoes enolization, one of the asymmetric centres present in this compound disappears, and when the enol form reverts to the keto form, it can do so to produce not only the original keto molecule but also the keto form in which the configuration of the bottom asymmetric carbon atom is opposite to that in the original ketone:



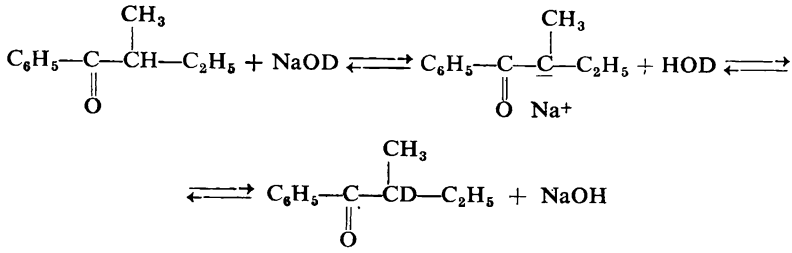
The conversion of menthone into isomenthone shown in the above scheme proceeds particularly readily in the presence of alkalis; in this, just as in other cases, the racemization is catalysed by the same agents that catalyse the enolization — hydroxyl and hydrogen ions. The enolization mechanism of racemization was regarded several decades ago as a rather general one, but at present it is not thought so. Many of the cases of racemization which were formerly considered to be the result of enolization, are now treated in a different manner. The neighbourhood of the carboxyl, carbonyl, nitrile, and a number of other groups, while increasing the acidity of hydrogen in the α-position, can facilitate the formation of a carbanion and lead to racemization (base-induced racemization) of compounds such as mandelic acid XXXVI, the homologues of acetophenone XXXVII, and ketones of the type XXXVIII:



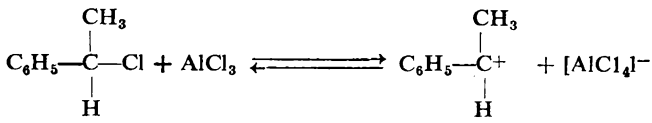
XXXVI XXXVII XXXVIII

In particular, the rate of racemization of ketones of the type XXXVIII decreases in those cases when the radical R′ has electron-donating properties and thereby reduces the tendency for the hydrogen atom attached to the asymmetric centre to undergo ionization (84). That the rate of racemization of *sec*-butyl phenyl ketone in dioxan-deuterium oxide solution in the presence of NaOD is the same as the rate of deuterium exchange is evidence that both processes occur via the same intermediate

product. The formation of the carbanion but not of the enol is now believed to be common to both reactions (85):



Racemization may also take place under the influence of heat (thermal racemization): the bond between the asymmetric atom and one of the substituents is broken homolytically under the influence of thermal energy. The radical formed may assume either of the two enantiomeric configurations with equal probability on recombination, i.e., a racemate is formed. For instance, α-phenylethyl chloride, $C_6H_5—CHCl—CH_3$, undergoes thermal racemization in the course of distillation. The same compound when acted on by Lewis acids racemizes by a different mechanism — with the intermediate formation of a carbonium ion:



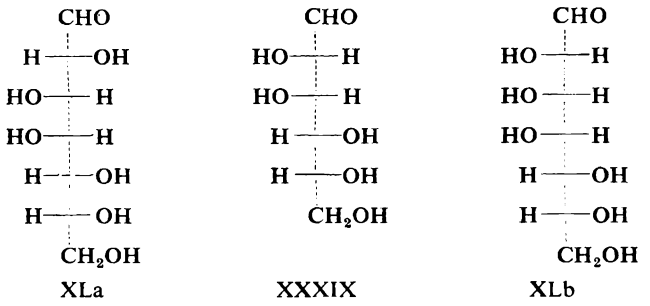
It is important to remember that in practical work with optically active substances one may encounter racemization in the course of reactions proceeding under mild conditions, which, one would think, leave the asymmetric centre untouched. Thus, for example, α-phenylethyl alcohol dissolved in liquid sulphur dioxide is racemized even at room temperature (probably, via the formation of carbonium ions) (86). Another case of racemization under mild conditions is the loss of optical activity by α-phenylethyl chloride when it is subjected to chromatographic separation on silica gel (87). No racemization has been observed on another adsorbent, alumina.

## 2.9. ASYMMETRIC SYNTHESIS AND ITS TYPES

Asymmetric synthesis is the second most important method of preparing optically active substances. Asymmetric synthesis involves stereospecific reactions, as a result of which the enantiomers are formed or destroyed

in unequal amounts. Recall that the resolution of racemates leads to the *separation of optical antipodes* (enantiomers); in asymmetric synthesis the two antipodes *are formed* in such a manner that the predominance of one of them in the reaction products gives rise to optical activity.

In the course of his studies of sugars Emil Fischer (1894) found that the various transformations of sugars, which were accompanied by the appearance of a new asymmetric centre, usually resulted in the formation of only one of the two possible stereoisomers. For example, the synthesis of heptose from mannose XXXIX via cyanohydrin gives rise to only one of the two possible configurations of the new asymmetric centre (compounds XLa and XLb):




Thus, the asymmetry present in the original mannose exerts a certain directing effect during the formation of a new asymmetric centre. It is for the processes of this kind that E. Fischer coined the term "asymmetric synthesis", indicating that if the "old" asymmetric centres (those already present in the molecule) could be separated from the newly formed one, a new optically active compound would be obtained.

The effectiveness of asymmetric synthesis is estimated by the optical purity of the product obtained, but usually the term **optical yield** is used in application to asymmetric synthesis: these two quantities are numerically equal. The first asymmetric syntheses carried out at the beginning of this century had a low optical yield and were only of historical importance. Many of the asymmetric syntheses with high optical yields, which have been accomplished in recent years, have become practically important as methods of preparing optically active compounds.

The following types of asymmetric synthesis are distinguished at present:

1. **Partial asymmetric synthesis,** which is effected through the intermediate use of auxiliary optically active compounds produced by living nature. Versions of asymmetric synthesis are kinetic transformations and kinetic resolutions (see below).

2. **Absolute asymmetric synthesis** which includes processes leading to the formation of optically active substances without the intermediate use of optically active reagents or any other factors dependent on living

nature. An extension of absolute asymmetric synthesis is asymmetric catalysis on optically active quartz.

In what follows we shall speak of partial asymmetric synthesis, omitting the word partial; the term absolute asymmetric synthesis is used fully where necessary.

Asymmetric (partial asymmetric) synthesis may be the result of the various chemical transformations proceeding through the mediation of optically active auxiliary substances: these may be substitution, elimination, and addition reactions in the course of which a new asymmetric centre is created. An intermediate (in a certain sense) position between the resolution of racemates and the asymmetric synthesis is occupied by processes which involve the "activation" of racemates through kinetic transformations or kinetic resolution (see below). We shall first consider these processes before taking up a discussion of the various types of reactions of asymmetric synthesis.

## 2.10. ASYMMETRIC TRANSFORMATIONS AND KINETIC RESOLUTION

The phenomenon of racemization which has been discussed above shows that in certain cases there may occur a change in the spatial arrangement of the substituents about an asymmetric centre. In racemization, such a process leads eventually to the formation of an equimolecular mixture of optical antipodes—a racemate:

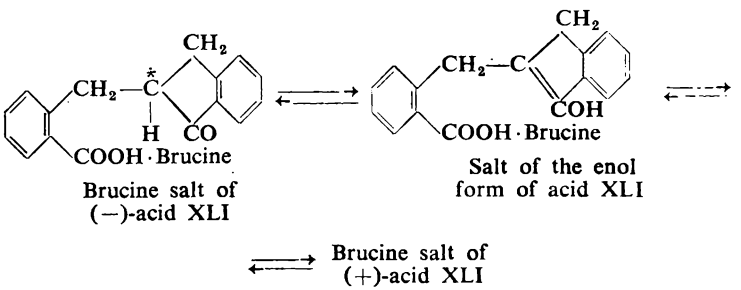
$$\underset{100\%}{(+)\text{-A}} \longrightarrow \underset{50\%}{(+)\text{-A}} \cdot \underset{50\%}{(-)\text{-A}} \longleftarrow \underset{100\%}{(-)\text{-A}}$$

But if the process involving a change in the configuration of the asymmetric centre occurs under the influence of other elements of chirality present in the substance itself or in its environment (solvent, catalyst), then the moment of attainment of the equilibrium must not necessarily coincide with the formation of an equimolecular mixture of both enantiomers: under the influence of the second chiral centre or chiral medium one of the forms (one of the diastereomers in the first case and one of the antipodes in the second) may prove more favourable than the other. In this case, starting with a racemate, it is possible to prepare mixtures of the enantiomers with a preponderance of one of them: in principle, the process we are speaking of is the converse of racemization. Such processes are termed **asymmetric transformations.**

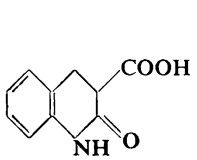
A distinction is made between *first-order* asymmetric transformations, in which a shift of the equilibrium to the side of formation of one of the enantiomers is observed in solutions, and *second-order* asymmetric trans-

formations, in which one of the optical antipodes crystallizes from solution and, hence, there may take place a complete conversion of the racemate into one of the optically active forms.

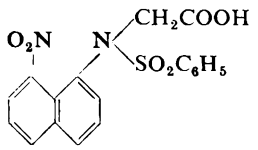
One of the long-known examples of such "activation" of a racemate was observed in 1905 by Marckwald on prolonged heating of racemic mandelic acid with brucine: mandelic acid was prepared, which had a small optical rotation. Another case was described in the early 1920s by Leuchs. From the brucine salt XLI there was isolated, on slow acidification, a free acid entirely in the (+)-form, which is the result of the displacement of the equilibrium in the racemate under the influence of brucine:



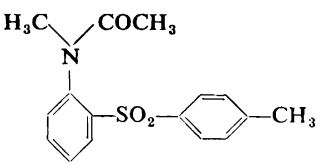

The analogous behaviour is shown by acid XLII which when reacted with quinidine in methanol is entirely converted into the dextrorotatory form with an [α] value of +56.4°. Both optically active substances (XLI and XLII) readily undergo racemization: when the free acids are allowed to stand, their rotation soon falls to zero. Phenomena of the same kind have also been observed with compounds XLIII and XLIV, whose optical activity is caused by atropisomerism:




XLII




XLIII




XLIV

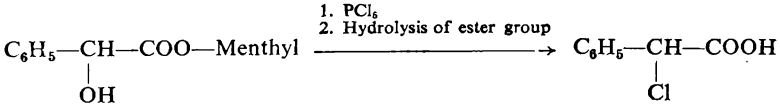
In certain transformations, optical antipodes react with *different* velocities. This is observed either in reactions proceeding in the presence of optically active catalysts or in reactions with optically active substances. If a racemate is introduced into such a reaction and the transformation is stopped before completion, one of the antipodes will react more rapidly and will predominate in the reaction product, and the second will prevail in the unreacted residual product. In this way, a kinetic resolution of the racemate can be achieved.

Racemic mandelic acid undergoes kinetic resolution in the reaction with menthol: the ratio of the reaction rates for the (—)- and (+)-forms is equal to 0.897. A kinetic resolution also takes place in the course of the reaction of racemic α-phenylethylamine with (—)-quinic acid; a residual amine is also obtained, which has an optical rotation of +3.5°, which corresponds to an optical purity of about 10 per cent. Racemic mandelic acid undergoes kinetic resolution also in the reaction with (—)-menthylamine: the ratio of the reaction rates for both antipodes is 0.862.

Still another case of kinetic resolution is furnished by the work carried out by Wegler who showed that the esterification of racemic α-phenylethyl alcohol by an amount of acetic anhydride that is insufficient for complete conversion, in the presence of brucine yields an optically active ester with $[\alpha]^{20}_{578}$ equal to 33.4°, which corresponds to an optical purity of the order of 25 per cent. The rotation is particularly high if the racemization reaction is conducted slowly, at a decreased temperature. An analogous asymmetrizing effect is exerted by the presence of brucine on the reactions of α-phenylpropyl alcohol with hydrogen chloride and of α-phenylethylamine with phenyl isocyanate.

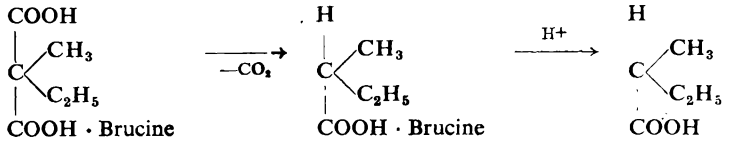
The action of carbon dioxide on the optically inactive organomagnesium compound prepared from 2-chlorobutane, with (+)-2,3-dimethoxybutane used as the solvent, gives levorotatory 2-methylbutanoic acid.

In all the cases considered above, there was an asymmetric centre present in the substance and the task was basically to resolve the racemate by taking advantage of the differences in the velocities with which the antipodes reacted. Asymmetric synthesis of a somewhat different type—in the course of a substitution reaction at a chiral centre—was observed in the conversion of the menthyl ester of racemic mandelic acid into phenylchloroacetic acid. The optical purity of the latter compound amounted to 5 per cent:



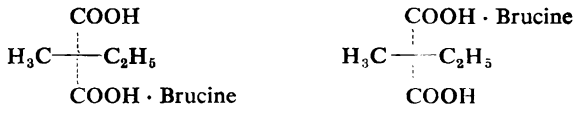

A case of kinetic resolution is the reaction carried out in 1904 by Marckwald, namely the decarboxylation of the half-brucine salt of ethylmethylmalonic acid, which resulted in the formation of optically active

ethylmethylacetic acid. This is also, in principle, the result of a substitution reaction at the asymmetric centre, which proceeds with different rates for both antipodes:



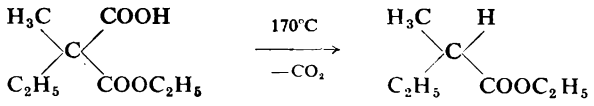

The magnitude of rotation of the acid obtained was only —1.7°, which corresponds to the 10 per cent excess of the levorotatory antipode.

This synthesis has been used for a detailed study of the mechanism by which the reaction product becomes optically active. Marckwald himself believed that when the solution of the half-brucine salt of ethylmethylmalonic acid was evaporated, of the two possible diastereomers, XLVa and XLVb, only one was predominantly formed, and the decarboxylation proceeded then across the free carboxyl group not linked to brucine.




XLVa XLVb

Kenyon and Ross, however, showed that this is not that simple (88). It was established that the decarboxylation of the acid ethyl esters of optically active substituted malonic and cyanoacetic acids (ethylmethylmalonic, ethylcyanoacetic, α-benzyl-α-cyanopropionic) gives optically inactive reaction products:

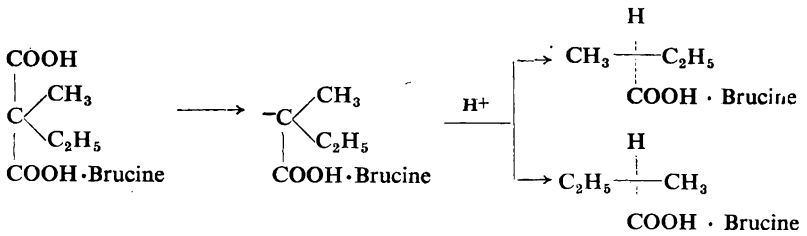



XLVI

It has been conclusively proved that the racemization actually takes place in the course of the reaction and that the ester itself, XLVI, is not racemized even on prolonged heating. Having arrived at this conclusion, the authors then carried out the decarboxylation of a number of salts of acid esters of ethylmethylmalonic acid with different alkaloids; the resulting ethylmethylmalonic acid was found to be optically inactive in this case too.

The following explanation was eventually given to account for all these facts. In the asymmetric synthesis according to Marckwald, the carbanion XLVIII formed from compound XLVII can produce, as a

result of its combination with a proton, two diastereomers which differ in the configuration of the newly created asymmetric centre:




XLVII XLVIII

It is known that diastereomers have different energy characteristics and are formed at different rates and therefore the formation of a certain excess of one of them is quite understandable. The situation is different with the decarboxylation of compound XLVI: the intermediate carbanion here has no optically active substance; when a proton is added, the carbanion forms, with equal probability, both antipodes, i.e., a racemate is formed. According to this mechanism, the dibrucine (normal) salt of ethylmethylmalonic acid must also give optically active methylethylacetic acid on decarboxylation. The experiments conducted have supported this prediction.

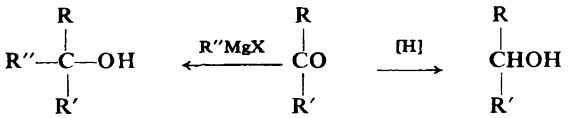
Asymmetric decarboxylation has been used to prepare optically active deuterium-containing compounds according to the following scheme:

The thus obtained acids with hydrogen-deuterium asymmetry have very small values of rotation (of the order of 0.006-0.030°), which is due not only to their low optical purity but also to the well-known fact that compounds with hydrogen-deuterium asymmetry have, in general, small angles of rotation.

Kinetic resolution was also observed in reactions of 2-phenylbutylmagnesium chloride with optically active ketones (89): when the reaction was conducted with an insufficient amount of (—)-menthone, the 2-phenylbutylmagnesium chloride left was found to be optically active, which was proved by its decarboxylation into (—)-3-phenylpentanoic acid having an optical purity of the order of 10 per cent. An optically active product was also obtained in an analogous reaction with racemic ketone but in the presence of an optically active solvent, (+)-2,3-dimethoxybutane (90).

## 2.11. CREATION OF AN ASYMMETRIC CENTRE FROM THE CARBONYL GROUP

Partial asymmetric syntheses involving the formation of a new asymmetric centre are often effected by way of conversion of a carbonyl group into a secondary- or tertiary-alcoholic group by the following scheme:



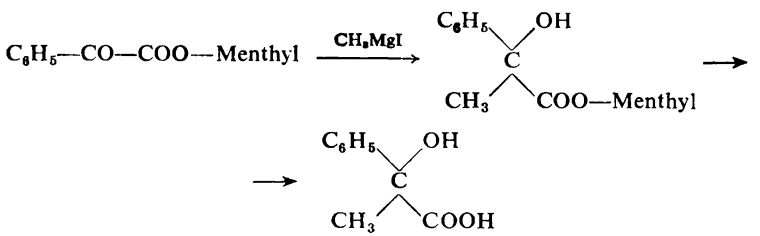

### 2.11.1. SYNTHESES BASED ON α-KETONIC ACIDS

One of the much-favoured objects for asymmetric syntheses is benzoylformic (phenylglyoxylic) acid, $C_6H_5COCOOH$. Two variants of asymmetric synthesis are possible in principle for this and other ketonic acids: (1) an auxiliary optically active substance is introduced into the molecule of the acid (esters with menthol have been most often used up to now); or (2) the asymmetrizing effect is exerted by an optically active reagent.

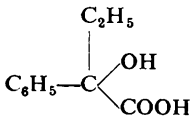
The first variant may be illustrated by a number of partial asymmetric syntheses carried out by McKenzie (1904). For example, benzoylformic acid was esterified with (—)-menthol, the ester (menthyl benzoylformate) reduced with aluminium amalgam, and the resulting product hydrolysed; the mandelic (atrolactic) acid so obtained was found to be optically active:

$$C_6H_5—CO—COO—Menthyl \longrightarrow C_6H_5—CHOH—COO—Menthyl \longrightarrow$$
$$\longrightarrow C_6H_5—CHOH—COOH$$

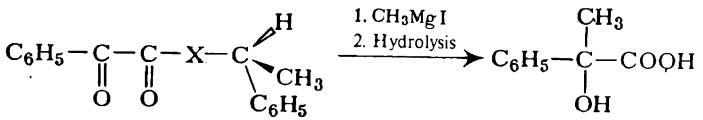
If the same starting compound is allowed to react with organomagnesium compounds, an asymmetric synthesis occurs, which involves the formation of a tertiary-alcoholic group:



The atrolactic acid so obtained had $[\alpha]_D$ of —9.5°, which corresponds to an optical purity of 25 per cent. A similar synthesis involving the bornyl ester of phenylglyoxylic acid (bornyl phenylglyoxylate) and ethylmagnesium iodide led to the related optically active acid

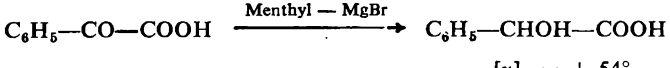


At a later time there was carried out a comparative study of the asymmetric synthesis of atrolactic acid by the action of methylmagnesium iodide on the esters or amides of benzoylformic acid into which the optically active α-phenylethyl radical was preliminarily introduced:




With the α-phenylethyl residue having the configuration indicated in the above scheme, the esters (X = O) give atrolactic acid having predominantly the S-configuration (dextrorotatory) and the amides (X = NH) afford atrolactic acid with a preponderance of the R-antipode (91).

The second route involving the participation of optically active reagents may be illustrated by syntheses in which sterically hindered optically active organomagnesium compounds were used as reducing agents. For example, optically active menthylmagnesium bromide was employed:




$[\alpha]_D = + 54°$
(optical purity 35%)

It was natural to assume that in the presence of auxiliary asymmetry both in the starting material and in the reagent it is possible (with appropriate configurations of "directing" asymmetric centres) to increase the optical yield. This idea was first tested by the action of optically active menthylmagnesium bromide on (—)-menthyl phenylglyoxylate; the mandelic acid obtained had an optical purity of 43 per cent, which was higher than that of the acid produced by the action of each of the asymmetrizing factors separately. This procedure was studied more thoroughly at a later time (92). It was shown that if ethyl phenylglyoxylate is reduced with a complex of lithium aluminium hydride with three molecules of

(—)-menthol, the resulting mandelic acid will have a low optical purity; but when (—)-menthyl phenylglyoxylate is reduced, the optical purity of the reaction product increases by 10 times — up to 40 per cent.

### 2.11.2. PRELOG'S RULE

While studying the problem of asymmetric synthesis, scientists were naturally interested in the factors responsible for the occurrence of asymmetric syntheses and in their mechanism. The first assumptions in this respect were general. Thus, in the well-known book by Freudenberg (93), the following three plausible mechanisms of partial asymmetric syntheses are discussed:

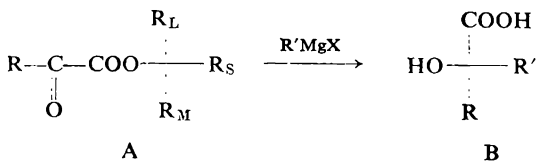
1. An auxiliary asymmetric reagent exerts an effect on the molecules being converted, so to say, at a distance, directing sterically the conversion in a certain manner. This concept is known as **asymmetric induction**; it was put forward in the works of Erlenmeyer.

2. First there appear equal amounts of the dextro- and levorotatory forms, but then the equilibrium between these forms is displaced because of the presence of an asymmetric reagent. Here we are actually dealing with asymmetric transformations, which have already been discussed above.

3. A new asymmetric centre is created in a molecule which already possesses asymmetry due to the presence of an optically active auxiliary asymmetric reagent. Here the asymmetric character of the synthesis is directly associated with the fact that diastereomers (and in this case diastereomers are always formed first) possess different energy reserves and are therefore formed at different rates.

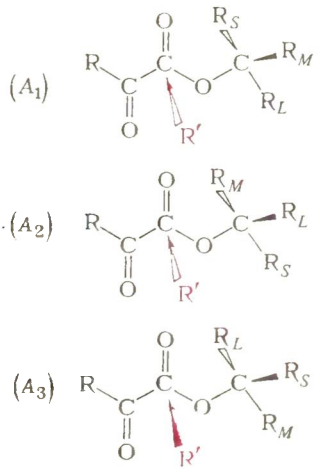
All these explanations, though in a general form, provide an answer to the question *why* asymmetric synthesis does actually take place but fail to throw light on the *course* of the asymmetric synthesis. The present-day conception of the mechanism of asymmetric syntheses is entirely based on *conformational analysis*. This approach was first suggested by Prelog in the fifties (94) for the case of asymmetric syntheses effected by the interaction of organomagnesium compounds (Grignard reagents) with the esters of α-ketonic acids and optically active alcohols.

**Prelog's rule** states that if an optically active alcohol used as a directing asymmetric reagent has the configuration A, a hydroxy acid of predominating configuration B is formed:



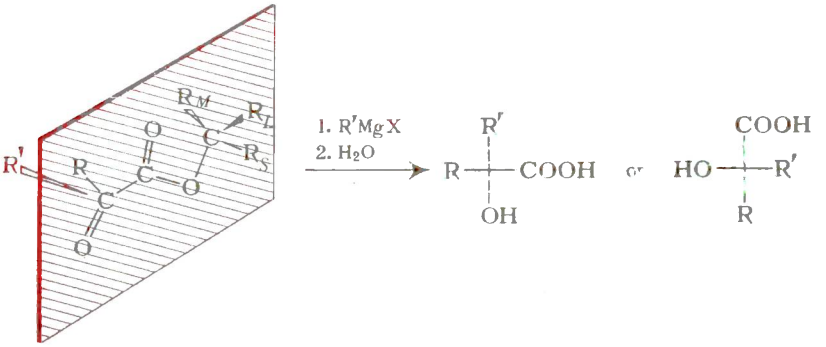
The symbols $R_L$, $R_M$, and $R_S$ denote here the large, medium-sized, and small groups of the directing asymmetric reagent; R is the radical of the keto acid; R′ is the radical of the organomagnesium compound (Grignard reagent).

The regularity noted was interpreted by Prelog on the basis of conformational analysis as follows. He believes that the most stable conformation of the grouping —CO—CO—O— is a planar conformation in which the two carbonyl groups are *trans* to each other. As a result of the rotation about the O—$\overset{*}{C}$ bond the optically active asymmetric alcohol may arrange itself in three ways. So, three conformations should be considered for the starting ester, which are regarded by Prelog as equally probable:

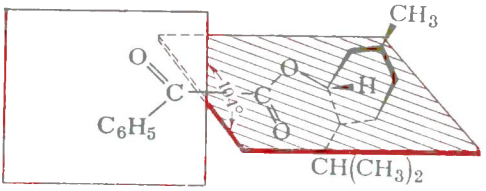



The configuration of the newly created asymmetric centre depends on the direction of approach of the radical of the organomagnesium compound to the carbonyl group. The sides of the C=O group are diastereotopic in this case and the two directions of approach—from the front or from behind the plane of the drawing—are not equivalent. The more favourable approach in conformation $A_1$ is from behind since the approaching radical R′ is sterically hindered in this case from the side of the *small* group attached to the asymmetric centre (and not of the medium-sized group as it could have been upon approach from the front). The same direction of approach is also preferential for conformation $A_2$, whereas for conformation $A_3$ the preferential attack is from the front. If all the conformations are considered to be equally probable, the attack from behind is found to be preferential, which leads to the con-

figuration specified by the rule. For conformation $A_2$, this may be depicted by the following scheme:



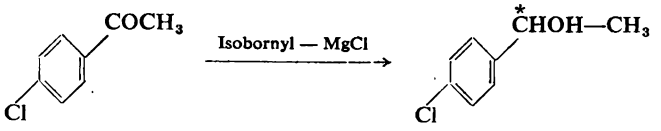

The application of Prelog's rule to analogous asymmetric syntheses has enabled configurations to be assigned to a variety of molecules. Examples are 1-*tert*-butylethanol, hydroxyl asymmetric centres in triterpenes and steroids. At the same time, the concrete model adopted in the rule was doubted by X-ray diffraction studies (95). From the results obtained it follows that in (—)-menthylphenylglyoxylate the two carbonyl groups, —CO—CO—, *do not* lie in an antiparallel manner in a single plane: they are almost perpendicular to each other. In such a model it is difficult to give preference to a certain definite approach of the reagent to the carbonyl group (to the attack from the front or from behind):



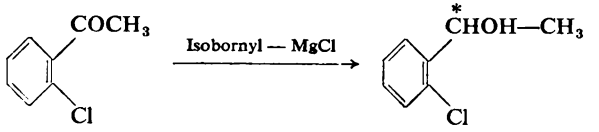
## 2.11.3. ASYMMETRIC SYNTHESES BASED ON KETONES

Asymmetric syntheses using ketones as the starting material proceed basically by the same routes followed by the asymmetric synthesis based on keto acids: the "directing centre" may be contained in the ketone or in reagent or else in the solvent.

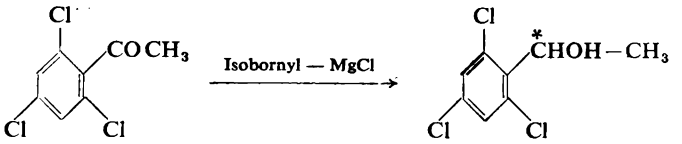
The first variant is realized in the reduction of unsymmetrical ketones by sterically hindered organomagnesium compounds (Grignard reagents); for example:




(optical purity 32%)



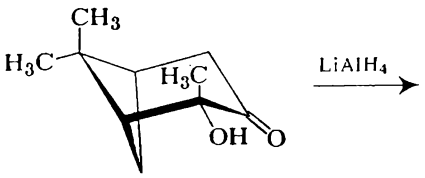

(optical purity 45%)



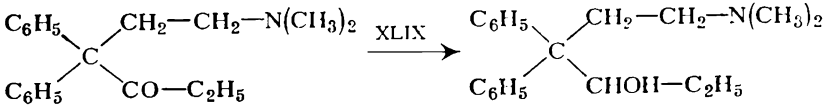

(optical purity 79%)

The increase in optical purity is accounted for in this case by the increase of steric hindrances in the original ketone because of the appearance of *ortho*-substituents in it. For a maximum optical yield to be secured, these (just as many others) asymmetric syntheses must be conducted under mild conditions, in the cold.

Optically active ketones when reacted with lithium aluminium hydride are reduced to the corresponding alcohols which exist as lithium complexes before they are decomposed by water: these complexes may in their turn serve as agents for the asymmetric reduction of other ketones. Examples are lithium complexes produced from (+)-hydroxypinocamphone (96):

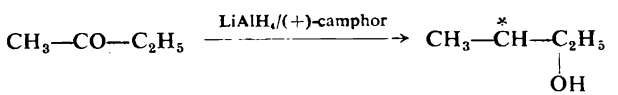



XLIX

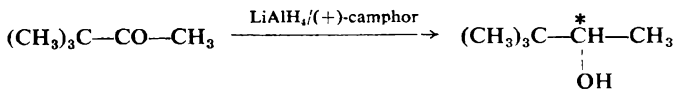


The optical yield is 2.9 per cent when complex XLIX is used and a *trans*-diol is formed, and 3.2 per cent when use is made of complex XLIX with the *cis*-diol being formed. The same complexes in the presence of benzyl alcohol (as the solvent) make it possible to increase the optical yields up to 13.2 and 32.8 per cent, respectively.

Asymmetric reduction is also observed when use is made of complexes formed from lithium aluminium hydride and camphor (more exactly, its reduction products):



$$[\alpha]_D^{25} = +2.50^\circ$$

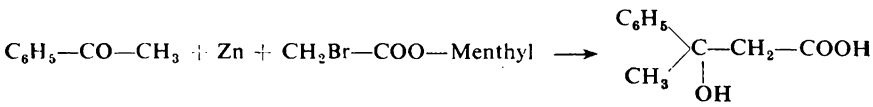


$$[\alpha]_D^{25} = +0.82^\circ$$

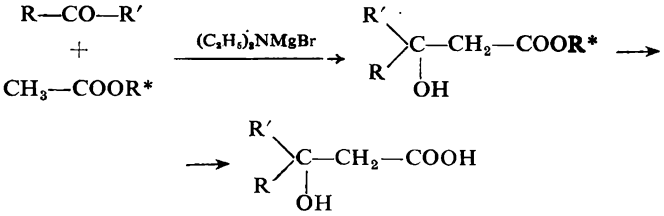
The optical purity in both syntheses ranges from 15 to 20 per cent. By conducting an analogous reaction as a "double asymmetric synthesis" (see page 121), it is possible to obtain mandelic acid having a higher optical purity (up to 49 per cent).

The asymmetric reduction of ketones and alcohols has also been effected by using complexes consisting of lithium aluminium hydride and other optically active alcohols (97), derivatives of carbohydrates (98), sparteine (99), amines (100).

Ketones can give optically active β-hydroxy acids in the Reformatsky reaction involving the esters of bromoacetic acid with optically active alcohols:

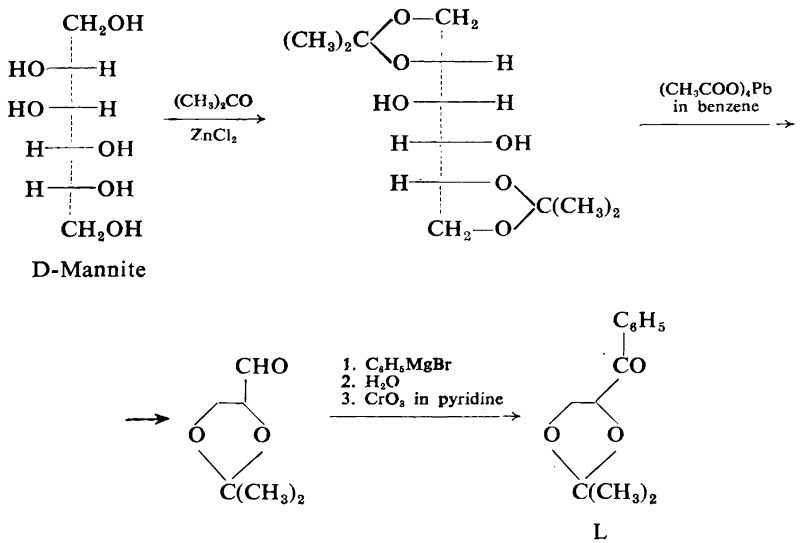


More thoroughly studied is the asymmetric synthesis of β-hydroxy acids from ketones by another variant of the method (101):



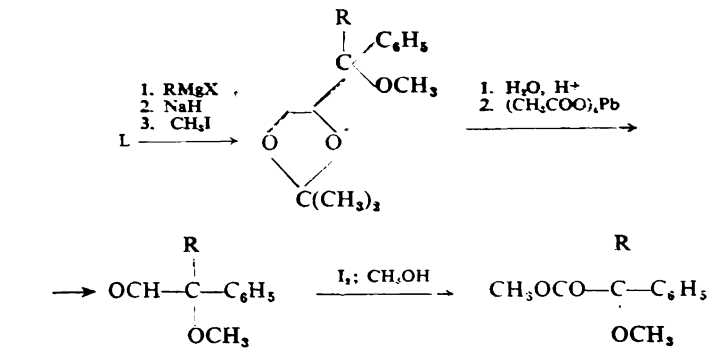
If the auxiliary asymmetric reagent is (—)-menthol, i.e., R* = menthyl, then the β-hydroxy acid formed in excess will have the S-configuration and the optical yield will amount to 70-90 per cent.

A high optical yield was also observed in the synthesis of α-methoxy acids (102) effected through the use of an asymmetric reagent L obtained by the action of lead tetraacetate on bis-isopropylidene-D-mannite. The synthesis of this reagent was accomplished by the following scheme:

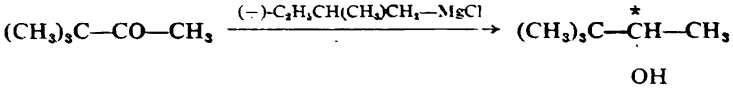


The reagent L was brought into reaction with an organomagnesium compound, the resulting alcohol was methylated and the asymmetric centre of the auxiliary reagent L was removed by a number of successive

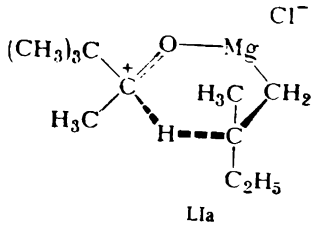
reactions: the α-methoxy acids so obtained had an optical purity of up to 98 per cent:



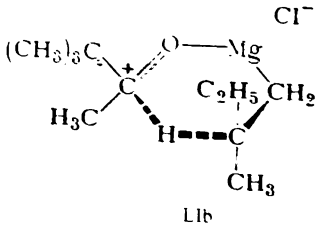
In the fifties, Mosher carried out a detailed study of the asymmetric reduction of pinacolin (pinacolone) by means of optically active Grignard reagents. The reducing agent in this case was (+)-2-methylbutylmagnesium chloride obtained from optically active amyl alcohol:



The optical rotation of the resulting pinacolyl alcohol was up to 1°, which corresponds to 16 per cent excess of the dextrorotatory isomer; the maximum stereospecificity was observed when the reaction was carried out at —75°C. The author explained the result (the appearance of optical activity) by postulating the formation of a cyclic six-membered transition state. The use of (+)-2-methylbutylmagnesium chloride may give rise to two transition-state complexes (LIa and LIb) which constitute, as it were, a pair of diastereomers differing in the configuration of the asymmetric centre formed from a carbonyl group:

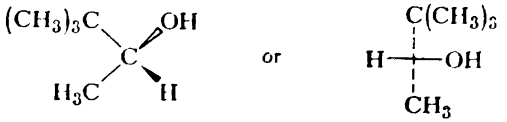


LIa

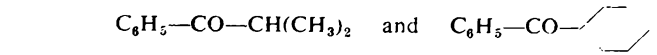


LIb

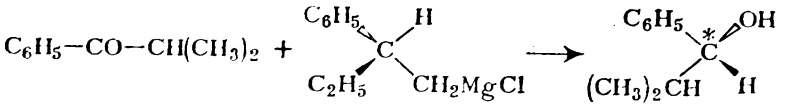
In the transition state LIa, the methyl group of the optically active Grignard reagent is on the same side of the six-membered ring as the *tert*-butyl group of the ketone; in the complex LIb, the *tert*-butyl group of the ketone and the ethyl group of the reagent are on the same side of the ring. In complex LIa, the groups that are on the same side of the ring create less steric hindrances to each other than the groups in complex LIb and therefore the preferred configuration is the one in the first complex, which is what predetermines the predominant configuration of the compound formed:




In subsequent years, the same reagent was employed for other ketones which contained a phenyl or cyclohexyl group instead of the *tert*-butyl group, and an alkyl radical, $C_2$-$C_4$, instead of the methyl group. The highest optical yield (24-25 per cent) was achieved with the ketones

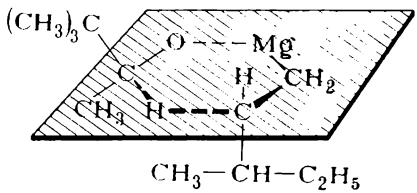



A point of interest here is that in both cases the molecule contains a phenyl group and a radical with a branch in the α-position to the carbonyl group, which creates considerable steric hindrances to the existence of the less favourable transition state. An even higher optical yield was attained by the use of an asymmetric reagent also containing a phenyl group: the optical purity of the resulting alcohol amounted to 82 per cent:

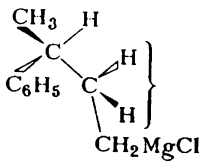



The spectacular model used to interpret the results of the asymmetric synthesis under consideration does not take into account all the factors contributing to the predominance of one of the antipodes. Thus, in the reduction of deuterated benzaldehyde, $C_6H_5COD$, and phenyl *tert*-butyl ketone, $C_6H_5COC(CH_3)_3$, the optical yield was found to be practically the same (about 19 per cent), though the steric requirements for the deu-

terium atom and for the *tert*-butyl group are sharply different (103). Besides, the model allows us to assume that the analogous reduction must not be asymmetric if the asymmetric centre of the Grignard reagent is separated from the MgCl group: in this case the asymmetric centre does not form part of the six-membered ring in the cyclic transition state. One of the hydrogen atoms of the $CH_2$ group will participate in the formation of the transition complex and there is always the possibility, independently of the configuration of the auxiliary asymmetric atom, to arrive at the sterically preferred complex:

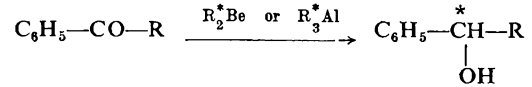



Checking-up of the consequence following from this reasoning first gave the expected result: the pinacolyl alcohol obtained by the action of 3-methylpentylmagnesium chloride on pinacolone was in fact found to be optically inactive. But other related asymmetric reagents, say, R-(—)-1-chloro-3-phenylpentane and R-(—)-1-chloro-3-phenylbutane (both in the form of the corresponding organomagnesium compounds), when reacted with phenyl isopropyl ketone led to the formation of optically active (+)-phenylisopropylcarbinol with an optical purity of 29 and 23 per cent, respectively. Since the asymmetric atom here does not form part of the six-membered cyclic transition state, the explanations given earlier do not fit in these cases. In connection with this, attention was drawn to the fact that the two possible transition states (which lead to the two enantiomeric reduction products) involve diastereotopic hydrogen atoms, which is sufficient for the two nonequivalence of the two transition states to be substantiated (a pair of diastereotopic hydrogen atoms, one of which participates in the hydride transfer, are marked).



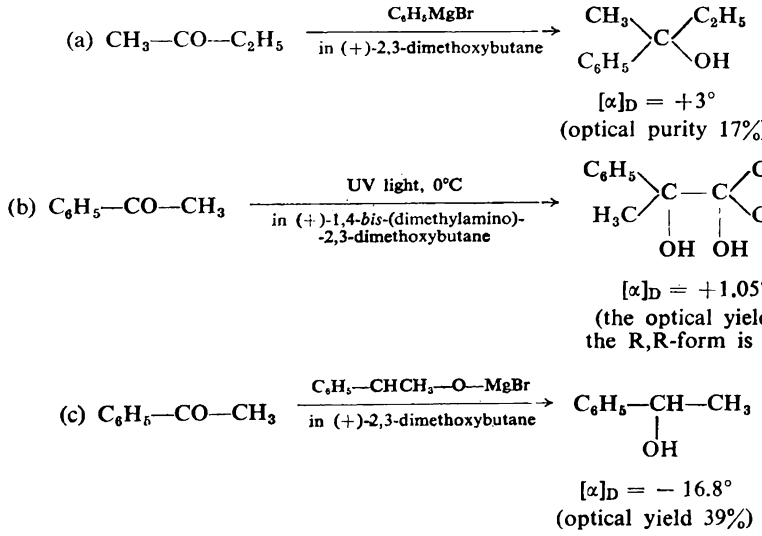
Not only organomagnesium compounds but also optically active organoberyllium or -aluminium compounds may be used as reducing agents for ketones:

These reagents have been used in the asymmetric reduction of arylalkyl ketones:



The optical yield increases with increasing bulkiness of the radical R: in going from the ethyl (13-15 per cent) to *tert*-butyl group (about 30 per cent). On the whole, the optical yield in such cases is about twice as high as in the use of the corresponding organomagnesium compounds (104).

Apart from the creation of asymmetry by the use of an optically active reagent, still another route has been found to be possible: the reaction may be conducted in optically active solvents. This has been demonstrated for the cases of organomagnesium (Grignard) synthesis [scheme (a)], pinacol reduction [scheme (b)] (105), and the attainment of an equilibrium of the Meerwein-Ponndorf-Verley reaction type [scheme (c)] (106).

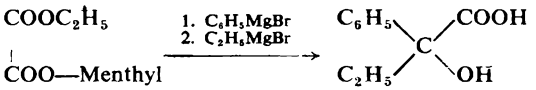


In the presence of asymmetric catalysts (alkaloids) it is possible to carry out the asymmetric synthesis of hydroxynitriles:

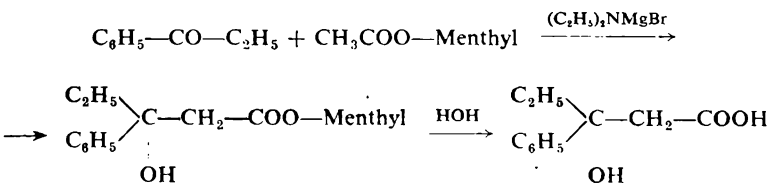
$$C_6H_5—CHO + HCN \xrightarrow{\text{alkaloid}} C_6H_5—\overset{*}{C}HOH—CN$$

Other aldehydes when condensing with hydrocyanic acid in the presence of quinine also give optically active hydroxynitriles with a rotation of up to 1°. Here an optically active catalyst has the same effect as the enzyme contained in bitter almonds, but the stereospecificity of enzymatic syntheses is manifestly higher. To illustrate, we may cite the results of the same synthesis effected in the presence of the enzyme D-hydroxynitrilase adsorbed by cellulose: the yield of mandelonitrile is 95 per cent and its optical purity is 97 per cent (107).

Optically active α-hydroxy acids have been synthesized by means of an organomagnesium synthesis involving the optically active menthyl ester of oxalic acid; an example is the following ($[\alpha]_{578} = -13.4°$; optical purity 38 per cent):

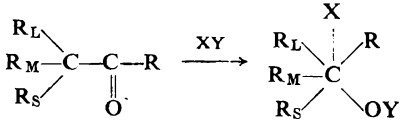


When propiophenone (the carbonyl component) was subjected to an aldol condensation with optically active menthyl acetate (the methylene component), there was observed the formation of optically active 3-hydroxy-3-phenylvaleric acid having an optical purity of 59 per cent (108):



2.11.4. CRAM'S RULE

**Cram's rule** (109) predicts the configuration of the diastereomer predominantly formed in the conversion of the keto group into an alcoholic group in reactions involving ketones which already contain an asymmetric centre in their molecules, i.e., in conversions of the following type:

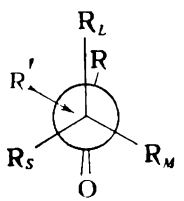


A new asymmetric centre is created here from the carbonyl group next to the asymmetric centre, and the structure of the compound is such that both chiral centres, the directing and the newly formed one, eventually remain within a single molecule.

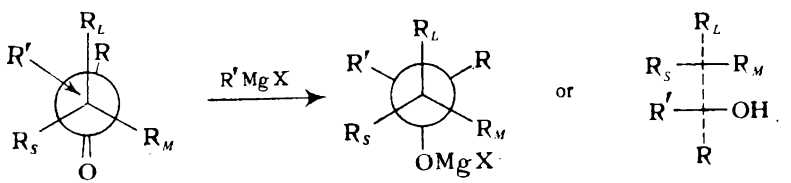
According to Cram's rule, the starting compound reacts in the conformation with the carbonyl oxygen being flanked by the two smaller groups ($R_M$ and $R_S$) attached to the adjacent asymmetric centre, and the diastereomer predominantly formed is that which results from the approach of the entering group from the *least hindered side* of the double bond (from the side of the smallest group $R_S$).

An example of the application of this rule is the following reaction:

where $R_L$, $R_M$, $R_S$ are, as before, the large, medium, and small substituents attached to the asymmetric centre. The preferred reaction conformation for the starting compound will be the following:

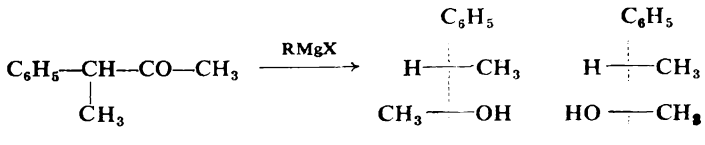


The configuration of the centre being formed will here depend on the side (the left or right on the drawing) from which the radical from R'MgX will approach the carbonyl carbon. Since the small substituent is on the left and the medium one on the right, the least hindered side is the left side. Hence, the predominant configuration of the product formed is LII:



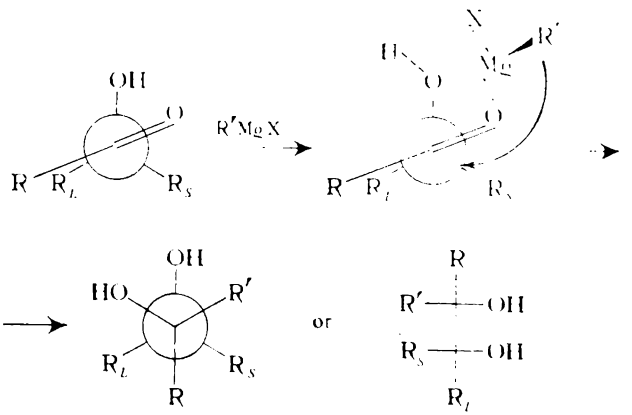

LII

It is worthwhile to stress once again that in these syntheses the stereospecificity manifests itself not in the creation of optical activity but in the predominant formation of one of the two possible diastereomers. The stereospecificity (the *erythro/threo* ratio) increases with increasing steric requirements on the part of the entering radical:



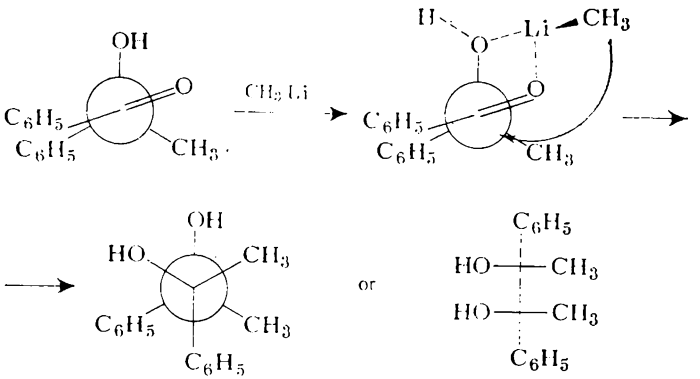
| | *threo* | *erythro* |
|---|---|---|
| R = $CH_3$ | 1 | 2 |
| $C_2H_5$ | 1 | 3 |
| $C_6H_5$ | 1 | 5 |

Apart from the "open-chain" model considered above, Cram suggested a different ("rigid") model (110) for compounds in which a hydroxyl or amino group is attached to the asymmetric carbon atom. An organometallic reagent (e.g. R′—Mg—X) first coordinates with both functional groups: as a result, they occupy the eclipsed position. Then the radical of the reagent attacks the carbonyl carbon from the side of the smaller of the two radicals attached to the asymmetric centre:

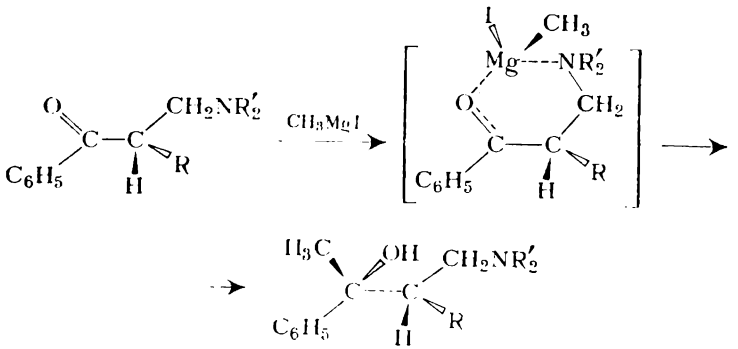


If the OH or $NH_2$ group is the medium-sized of the groups attached to the asymmetric centre (say, if $R_S = H$, $R_M = OH$, $R_L = C_6H_5$),

then the two models give the same result; but if the OH (or $NH_2$) group is the smallest of the three groups at the asymmetric centre, the use of the "open-chain" model leads to erroneous conclusions: the preferred diastereomer is correctly predicted only by the rigid model. For example, the major product of the following reaction is a *meso*-form and not a racemate:

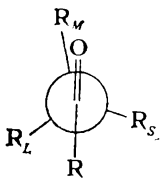



The rigid model also predicts successfully the configuration of the diastereomers formed by the action of Grignard reagents on Mannich's bases (111). To present this type of asymmetric synthesis, use is here made of a different projection in order to illustrate the frequently encountered method of representation of such asymmetric syntheses:

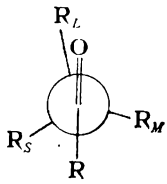



The "open-chain" model used by Cram was doubted in the works which appeared in the sixties, from which it follows that carbonyl com-

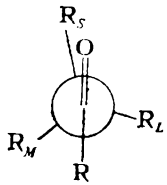
pounds exist in conformations in which the carbonyl group is eclipsed (112). Three such conformations are possible:



LIII



LIV



LV

Suggesting a new approach to the interpretation of Cram's rule, Karabatsos (113) rejects the third of the conformations given above (LV), believing that it is unfavourable because of the radical R being flanked by two relatively bulky radicals, $R_M$ and $R_L$. Of the two remaining conformations, LIII and LIV, Karabatsos considers the former to be the more preferred than the latter, the larger is the difference between their free energies. This difference is calculated on the basis of the interaction of the carbonyl oxygen with the large and medium-sized substituents attached to the asymmetric centre and is also determined experimentally from the ratio of the amounts of the reaction products formed from the diastereomers LIII and LIV (A and B, respectively):

$$G^{\neq}_{LIII} - G^{\neq}_{LIV} = -RT \ln \frac{A}{B}$$

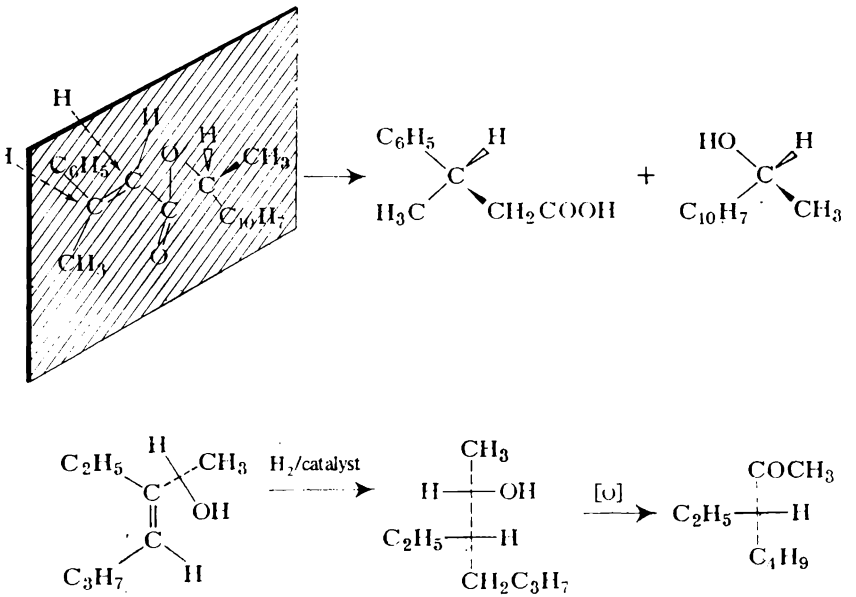
The calculated values were found by Karabatsos to be in good agreement with those determined from the ratio of the diastereomers produced in the synthesis. It should be noted that this new approach does not lead to the revision of Cram's rule: only a new different model is proposed for its interpretation. Apart from reactions with organometallic compounds, Cram's rule also applies to the reduction effected by the action of metal hydrides (114).

## 2.12. ADDITION TO THE CARBON-CARBON DOUBLE BOND

Addition reactions that take place across the carbon-carbon double bond constitute an important variant of partial asymmetric syntheses.

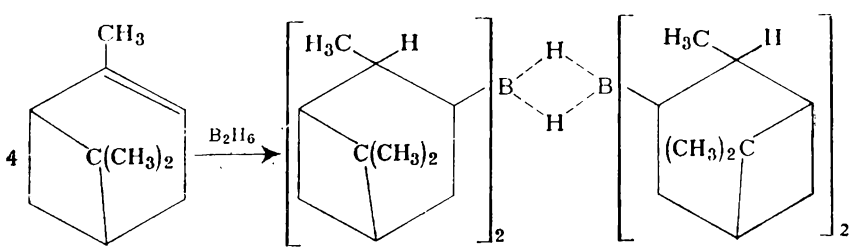
The *catalytic hydrogenation* of unsaturated acids in the form of esters with optically active alcohols is interpreted by Prelog on the basis of a model similar to the one proposed for asymmetric syntheses involving the esters of α-keto acids (see page 120). Thus, for instance, the ester

of β-methylcinnamic acid with optically active methyl-α-naphthylcarbinol become fixed to the surface of a catalyst in a conformation that provides a planar arrangement of all the groups, except the two substituents attached to the asymmetric centre. The side that approaches the catalyst is the one on which the less bulky substituent is arranged; the hydrogen leaving the catalyst also adds on from this side:



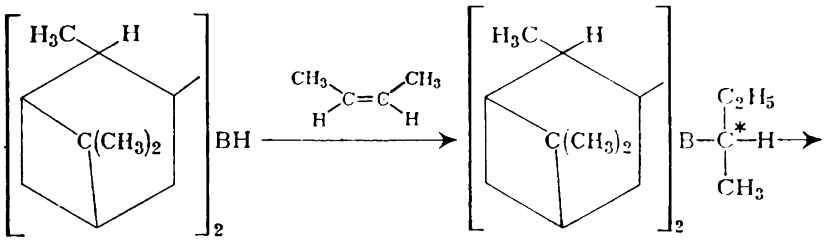
In the second of the examples given, the optical purity of the reaction product reaches 70 per cent.

Particularly high stereospecificity in addition reactions at the carbon-carbon double bond is achieved in hydroboration reactions effected by means of the reagent obtained from (—)-pinene:

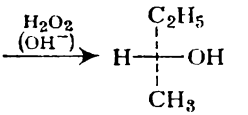


LVI

The action of diisopinocamphenylborane (reagent LVI in the above reaction; it is represented as a dimer since it usually exists in this form but hereafter we shall write it as the monomer for the sake of simplicity) on 1,2-*cis*-disubstituted ethylenes gives rise to hydroboration products which when oxidized by hydrogen peroxide are converted into optically active alcohols with an optical purity approaching 100 per cent (115). For example:



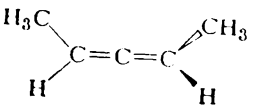
LVIa



R-(−)-2-Butanol

*trans*-Olefins and also olefins with a terminal double bond when reacted analogously afford alcohols having a low optical purity. Optically active amines can also be produced in a similar way (116).

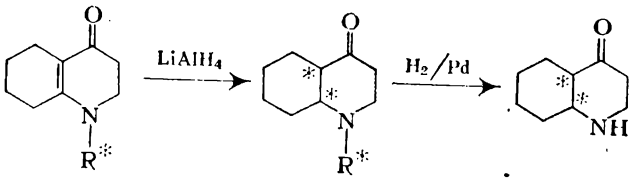
The same asymmetric reagent has been used to prepare optically active 1,3-dimethylallene: it has been found that when racemic 1,3-dimethylallene is subjected to hydroboration, the reaction predominantly involves one of the antipodes, the unreacted residue being found to be levorotatory. It has been proved that the following configuration corresponds to it:



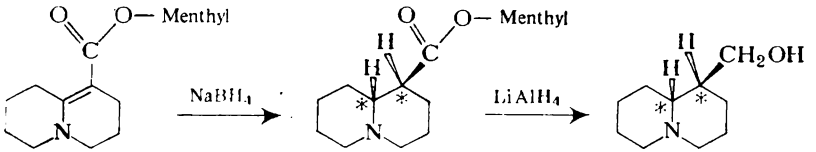
This is still another example of kinetic resolution (see page 115). Various models have been devised to account for the stereochemical features of hydroboration reactions; these models, like all the models discussed so far, are based on a consideration of the preferred conformations. These models are not discussed here; the reader is referred to the work of Streitwieser *et al.* (117).

Highly stereospecific is the reduction of the carbon-carbon double bond by lithium aluminium hydride in cyclic enamine ketones containing

an α-phenylethyl radical R* at the nitrogen atom. The optically active radical R* can be removed by subsequent hydrogenolysis and optically active decahydroquinoline produced (118):

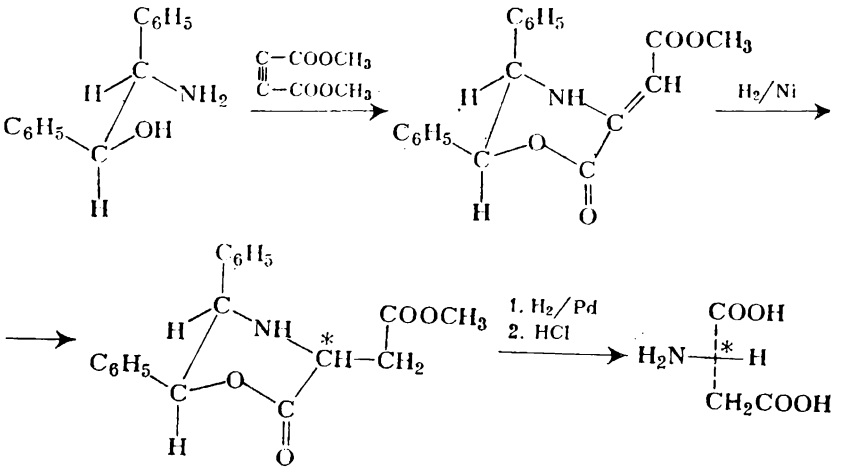



A similar asymmetric synthesis — the reduction of enaminoester — has been accomplished with the purpose of producing the alkaloid (+)-lupinine, but the optical yield was found to be low, of the order of 10 per cent (119):



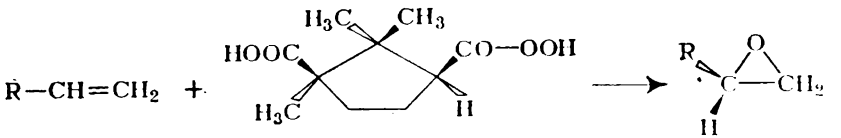

Asymmetric induction has also been observed in the alkylation of enamine ketones of the cyclohexanone series (120).

Highly stereospecific is the catalytic hydrogenation of the C=C bond in the asymmetric synthesis of aspartic acid (121):



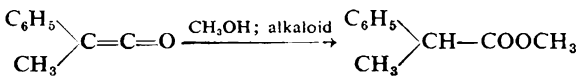
The aspartic acid obtained after hydrolysis is found to be optically pure.

A suitable agent for an asymmetric oxidation leading to the formation of optically active epoxy compounds is (+)-percamphoric acid. This compound has been used to prepare α-oxides with an optical purity of up to 4 per cent from a number of olefins with a terminal double bond, R—CH=$CH_2$ (where R = aliphatic radicals $C_1$ to $C_6$, cyclohexyl, phenyl):



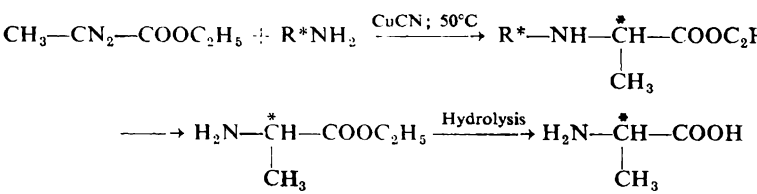
The asymmetrizing effect of percamphoric acid has also been observed in the oxidation of linalool (122); it has also been used in the synthesis of optically active isoquinoline alkaloids (123).

Asymmetric synthesis takes place in reactions of ketenes with optically inactive alcohols in the presence of alkaloids (124):



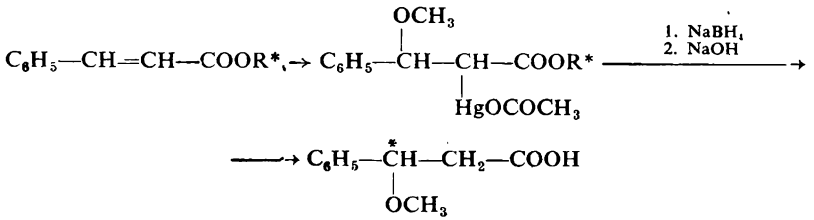
When (—)-α-phenylethylamine adds on to the phenyl methyl ketene, the process is also stereospecific. At —108°C the amount of the amide of (+)-α-phenylpropionic acid formed is 8 times greater than that of the amide of (—)-α-phenylpropionic acid. As the temperature increases the stereospecificity diminishes and becomes close to zero at +110°C.

Asymmetric syntheses involving carbenes have been described (125). When a carbene obtained from ethyldiazo propionate is incorporated across the N—H bond of optically active α-phenylethylamine, optically active alanine with an optical purity of up to 26 per cent can be obtained [R* = $CH(CH_3)C_6H_5$]:



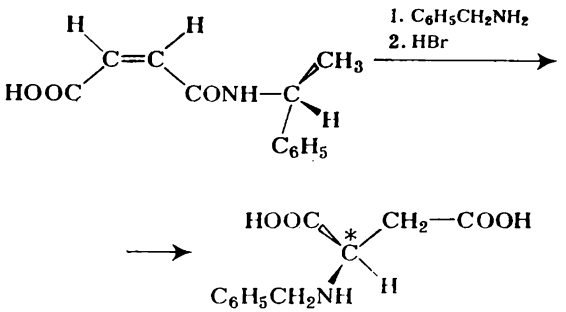
In a series of interesting works Kawana and Emoto have used widely distributed, readily available compounds such as sugars as auxiliary

optically active reagents. They have shown, in particular, that the methoxymercuration of the esters of cinnamic acid, $C_6H_5—CH=CH—COOR^*$ ($R^*$ is the sugar or terpene-alcohol residue) gives optically active 3-methoxy-3-phenylpropionic acid (126):

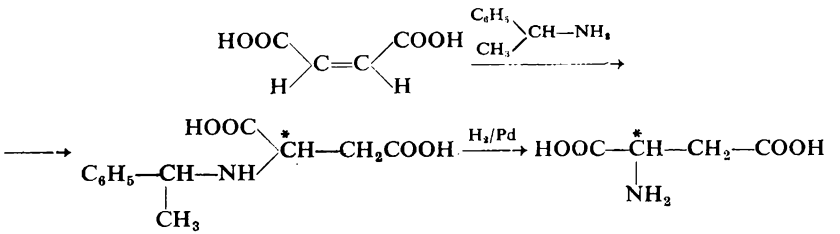



The addition of bromine to a carbon-carbon double bond in the presence of alkaloids leads to optically active 1,2-dibromides; analogous asymmetric syntheses have been described for cinnamic acid, cyclohexene, and 4-methylcyclohexene (127).

The addition of benzylamine to R-α-phenylethylmonoamide of maleic acid gives N-benzylaspartic acid of R-configuration in an optical yield of 60 per cent (128):

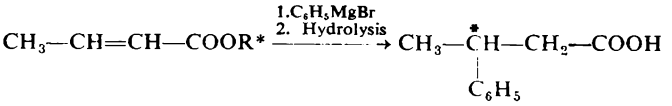



Terentiev and Gracheva have obtained optically active aspartic acid by the addition of (—)-α-phenylethylamine to maleic acid followed by the removal of the α-phenylethyl radical through hydrogenolysis (129):



Later, an analogous asymmetric synthesis was carried out by Japanese authors. Aspartic acid of high optical purity can be obtained, but a detailed study of the process has shown that no such effective asymmetric synthesis actually takes place here: the high optical purity of the reaction product is accounted for by the fact that of the two diastereomers of the intermediate only the less soluble one is isolated in the course of purification; it is this diastereomer which on hydrogenolysis gives optically active aspartic acid (see below, page 148).

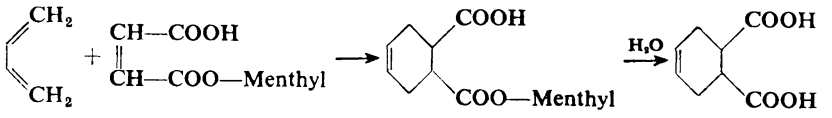
When phenylmagnesium bromide is reacted with the R-(—)-menthyl ester of crotonic acid, the product of the addition to the carbon-carbon double bond can be isolated. The product predominantly formed in this process is S-(+)-β-phenylbutyric acid in an optical yield of 5.4 per cent. If the same reaction is conducted in the presence of cuprous chloride, R-(—)-β-phenylbutyric acid is produced; the optical yield increases up to 10.2 per cent. When the menthol residue is replaced by the residue of di-1,2;5, 6-O-isopropylidene-α-glucose, the optical yield rises to 68 per cent (130):




From the cinnamate esters of sugars there have been obtained, on methoxymercuration, optically active β-hydroxy acids (131).

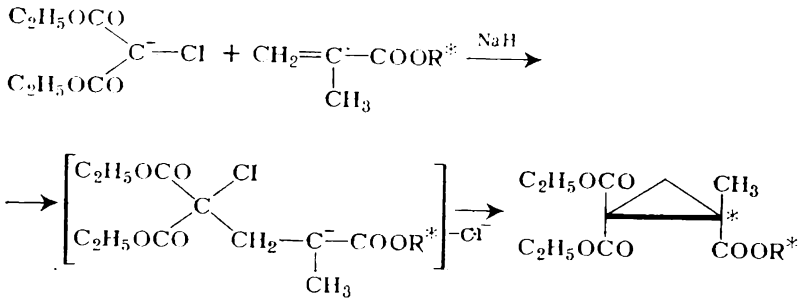
## 2.13. CYCLOADDITION REACTIONS

Korolev and Moore in 1948 described asymmetric diene synthesis for the case of the condensation of butadiene and chloroprene with the menthyl esters of fumaric or maleic acid. The highest rotation value ($[\alpha]_D^{20} = +11.65°$) was shown by tetrahydrophthalic acid produced by the hydrolysis of the condensation product of butadiene and optically active menthyl ester of maleic acid:




Analogous asymmetric syntheses were also carried out by other authors at a later time. In these works, the authors have noted the influence of temperature, pressure, and catalysts (Lewis acids) on the result.

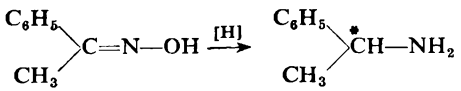
The asymmetric synthesis of cyclopropane compounds (in an optical yield of up to 7 per cent) has been effected by the reaction between menthyl methacrylate (R = optically active menthyl) and the carbanion formed from diethylchloromalonate (132):



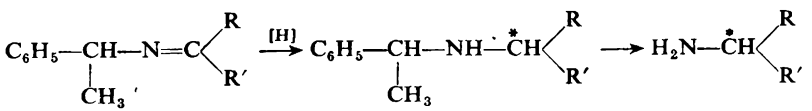
The analogous synthesis has been accomplished by the action of optically active menthyl α-chloropropionate on methyl methacrylate (133), in the Simmons-Smith reaction (by the action of a carbene from methylene iodide and zinc) on the menthyl esters of unsaturated acids (134). The optical yield is low, less than 10 per cent.

## 2.14. ADDITION TO THE CARBON-NITROGEN DOUBLE BOND

Asymmetric syntheses effected by addition to the carbon-nitrogen double bond have been used in several variations for the preparation of optically active amines and amino acids. In 1940 Nakamura carried out the asymmetric synthesis of α-phenylethylamine with $[\alpha]_D = +3.2°$ (8% optically pure) through the catalytic hydrogenation of acetophenone oxime in the presence of tartaric acid or (—)-menthyl hydroxyacetate:

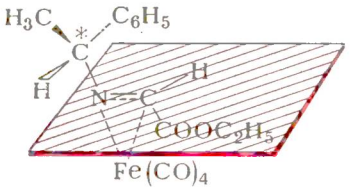


Another route for preparing optically active amines is by the hydroboration of Schiff's bases from optically active α-phenylethylamine with the subsequent removal of the α-phenylethylamine residue by hydrogenolysis (135):

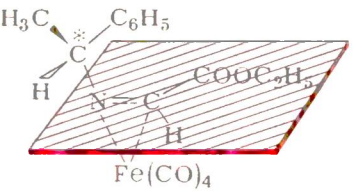


An optically active product is also formed in the electrolytic reduction of a Schiff's base from acetophenone and benzylamine in the presence of chiral salts (136).

Various asymmetric syntheses of this type have been repeatedly used for preparation of optically active amino acids. A high optical yield was achieved in carrying out such syntheses by means of diastereomeric metal-carbonyl-imine complexes (137). The reaction of (—)-α-phenylethylamine with ethyl glyoxylate and $Fe_2(CO)_9$ gives two diastereomeric complexes, LVII and LVIII (the latter obtained in predominance):

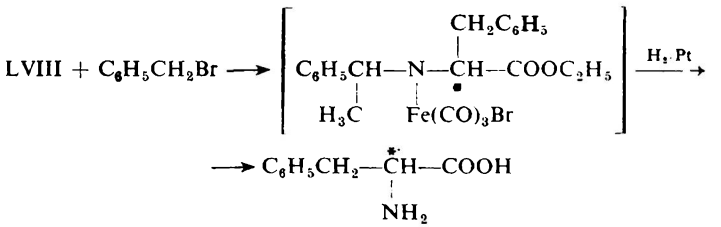



LVII



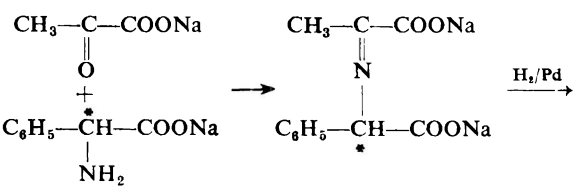

LVIII

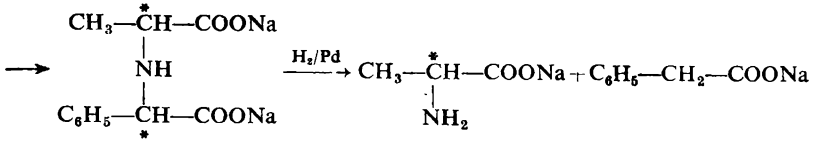
If complex LVIII is acted on by benzyl bromide, this being followed by hydrogenation, there will be formed L-(—)-phenylalanine 77% optically pure in 53% yield:



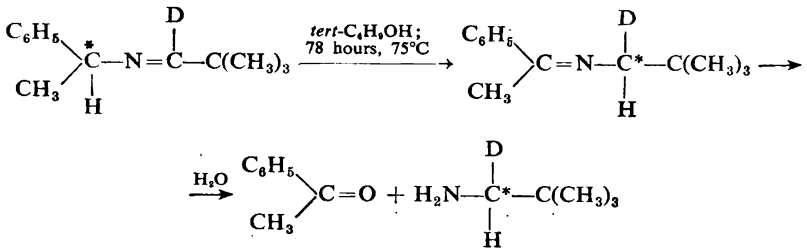

Such a result is attained only if the reaction between LVIII and benzyl bromide is conducted at a low temperature (35°C): when the temperature is raised up to 80°C, only a racemate obtains.

Mention should also be made of the transamination of keto acids, which is the model of analogous biochemical transformations. From pyruvic acid and L-phenylglycine there has been obtained L-alanine (41 per cent optically pure) according to the scheme (138):



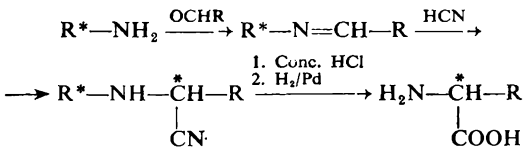


An asymmetric transamination of the intramolecular type also occurs in the isomerization of Schiff's bases from optically active α-phenylethylamine and deuterated aldehydes:

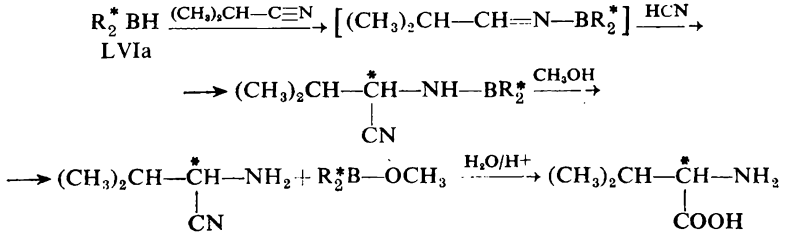


In the course of the reaction accompanied by the migration of the double bond and hydrogen, the optical activity is transferred from one centre to another almost without racemization (139).

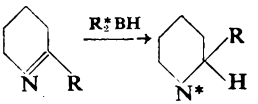
The asymmetric synthesis of amino acids has been effected by the addition of hydrogen cyanide to Schiff's bases obtained from optically active α-phenylethylamine [R* = $CH(CH_3)C_6H_5$] (140):



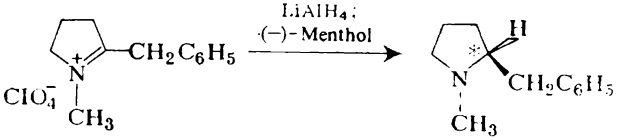
An asymmetric synthesis of amino acids has been suggested, in which use is made of optically active borane LVIa (see page 138) (141). The resulting R-(—)-valine has an optical purity of 12.4 per cent:



The hydroboration reaction effected by means of optically active reagents has also found application for other asymmetric syntheses proceeding due to the hydrogenation of the carbon-nitrogen double bond. The starting materials for such reactions are, for example, 2-disubstituted piperideines; the optical yield amounted to 24 per cent (142):

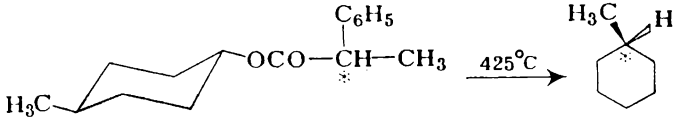



A further variant of asymmetric synthesis due to the hydrogenation of the double C=N bond is the preparation of optically active pyrrolidines by the action of lithium aluminium hydride in the presence of menthol on the salt of N-methyl-2-benzylpiperolinium (the optical purity of the product is 10.7 per cent) (143):




## 2.15. ELIMINATION REACTIONS

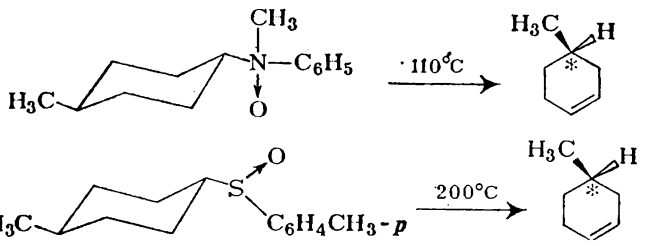
Several variants of elimination reactions have been employed for preparing optically active olefins. The pyrolysis of the R-(—)-*trans* ester of 4-methylcyclohexanol with optically active hydratropic acid (LIX) leads to the formation of R-(+)-4-methylcyclohexene having a very low optical purity (0.54 per cent) (144):




LIX

The optical yield is low probably because the directing asymmetric centre is far away from the ring in which asymmetry appears. The correctness of this assumption is supported by the fact that in the pyrolysis of compounds with an asymmetric centre directly attached to the ring, say, of an optically active amine oxide with an asymmetric nitrogen atom (145) or optically active sulphoxide with an asymmetric sulphur atom

(146), the optical yield is incomparably higher (the optical purity of the products is, respectively, 30 and 70 per cent):

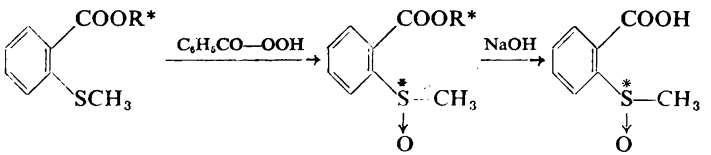



An asymmetric synthesis of this type has been used to produce *trans*-cyclooctene and in this way a new type of molecular asymmetry has been discovered.

## 2.16. ASYMMETRIC SYNTHESIS OF SULPHOXIDES

Several modifications of asymmetric synthesis have been used to prepare optically active sulphoxides — compounds with a sulphur atom as the chiral centre.

The esters of *o*-(methylmercapto)-benzoic acid with optically active alcohols after being oxidized by perbenzoic acid and saponified gave sulphoxides with an optical purity of up to 21 per cent:

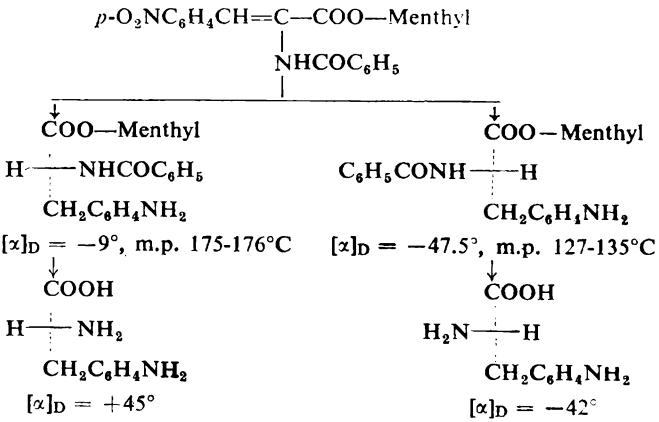



Another route to the preparation of optically active sulphoxides is by the oxidation of sulphides by means of (+)-percamphoric acid. A third pathway is the oxidation of sulphides with iodine in the presence of (+)-2-methyl-2-phenylsuccinic acid (147). A comparison of the results of this asymmetric synthesis (the optical purity achieved is 6 per cent) with the related biochemical oxidation of sulphides with the growing anaerobic culture *Aspergillus niger* (the optical purity achieved is 100 per cent) once again demonstrates the advantages of enzymatic processes (148).

The asymmetric synthesis of sulphoxides has also been effected via a cyclic intermediate obtained by the action of thionyl chloride on (—)-ephedrine (149).

## 2.17. ESTIMATION OF THE EFFICIENCY OF ASYMMETRIC SYNTHESES

In estimating the efficiency of asymmetric syntheses one should realize that the mere fact that a compound of high optical purity has been prepared does not necessarily point to the high stereospecificity of the asymmetric synthesis. Let us consider, in this connection, the work reported in the literature (150) which describes the preparation of optically pure *p*-aminophenylalanine. In this work, the optically active menthyl ester of α-benzoylamino-*p*-nitrocinnamic acid was hydrogenated over platinum supported on alumina. This reaction gave two diastereomeric menthyl esters of α-benzoylamino-*p*-aminohydrocinnamic acid. These diastereomers were separated from each other and saponified, as a result of which almost optically pure (+)- and (—)-*p*-aminophenylalanines were obtained:




Thus, the hydrogenation is followed by the process of resolution of the resulting racemate via diastereomeric esters with (—)-menthol. The asymmetry of the reduction reaction manifests itself only in the fact that the ester with m.p. 127-135°C is formed in an amount twice as high as the amount of the second diastereomeric ester; hence, the actual optical yield in the course of this reaction is about 33 per cent.

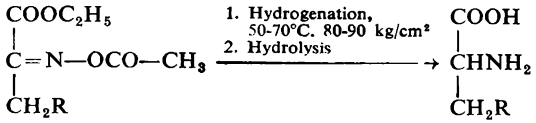
As has already been shown (see page 141), the analogous process of "secondary resolution" also accounts for the high optical purity of aspartic acid synthesized by the addition of optically active α-phenylethylamine to maleic acid.

Such processes of "secondary resolution" are possible only in those cases of asymmetric synthesis where the auxiliary optically active reagent

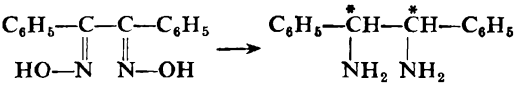
is contained in the reaction product formed and is separated from it only in subsequent transformations.

## 2.18. SYNTHESES WITH ASYMMETRIC CATALYSTS

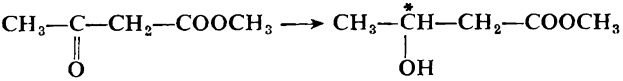
A promising method of preparing optically active substances is the conduction of reactions (mainly, hydrogenation reactions) in the presence of catalysts capable of exerting an asymmetrizing effect. A series of such syntheses have been accomplished by Akabori *et al.* in the fifties; he used a palladium catalyst supported on (optically active) silk fibroin:




With $R = CH_2COOC_2H_5$ the reaction product is glutamic acid ($R = CH_2COOH$) 8 per cent optically pure; with $R = C_6H_5$ there is formed phenylalanine with an optical purity of up to 30 per cent. A similar route was used to prepare stilbenediamine (7 per cent optically pure):




In the early sixties Izumi made an observation that asymmetrizing ability can be imparted to the skeletal nickel catalyst by treating it with an optically active substance prior to hydrogenation. Asymmetric syntheses based on the "modified" skeletal nickel catalyst became the subject of the extensive studies carried out by Izumi (151). The modifiers tested were various organic compounds possessing optical activity (tartaric acid, malic acid, amino acids), and the model reaction was almost exclusively the hydrogenation of methyl acetoacetate:

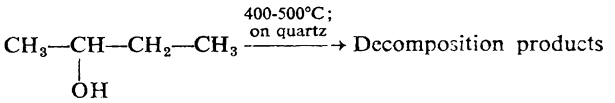



The modified skeletal nickel catalyst was also used for the hydrogenation of methyl ethyl ketone to the corresponding carbinol. The optical yield achieved in this reaction was 34 per cent.

The above-considered examples of catalytic preparation of optically active compounds belong to the category of partial asymmetric syntheses

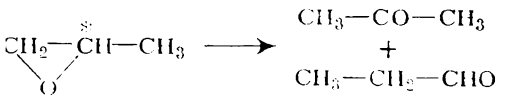
since natural organic asymmetrizing reagents are required for these reactions to be effected. There however exists a version of asymmetric catalysis, which is a case of synthesis known as *absolute* asymmetric synthesis.

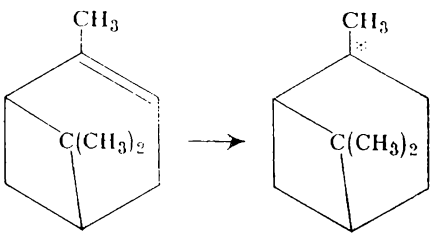
The possibility of carrying out asymmetric catalysis over dissymmetric crystals was pointed out as early as 1908 by Ostromysslensky, but the corresponding experiments were accomplished only in the early thirties by Schwab and his coworkers. Using optically active quartz as the support for a copper, nickel, or platinum catalyst, Schwab effected the asymmetric decomposition of 2-butanol, 3-methyl-3-heptanol and racemic menthol:




The residual alcohol assumed a rotation of the order of 0.13-0.25°, which corresponds to the optical purity of 0.6-1.1 per cent. The sign of rotation corresponds to that of quartz used as the support. The mechanism of the asymmetric influence is associated with the unequal adsorbabilities of the antipodes on optically active quartz: the antipode adsorbed more strongly is decomposed more rapidly (152), and therefore one of the antipodes accumulates in the residual product.

Interesting works on asymmetric catalysis using quartz have been carried out by Terentiev and Klabunovsky (153). Having repeated Schwab's experiments, these authors then extended them to other reactions and studied the isomerization of propylene oxide over an analogous catalyst (the maximum observed rotation of the residual product was $0.053 \pm 0.002°$), and the hydrogenation of racemic α-pinene (the reaction product was found to exhibit a rotation of up to 0.05°):



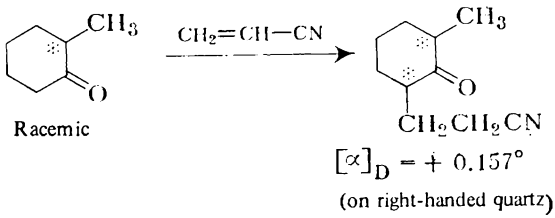


The last example is no longer an asymmetric destruction, unlike all the previous ones: this is a true asymmetric *synthesis*. This is also true of another reaction—the hydrogenation of ethyl α-phenylcinnamate:

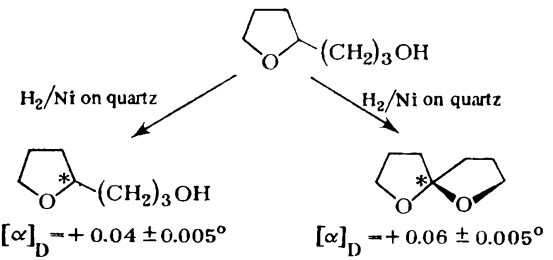
$$C_6H_5-CH=\underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{C}}-COOC_2H_5 \xrightarrow{H_2/Ni \text{ on quartz}} C_6H_5-CH_2-\overset{\displaystyle *}{\underset{\displaystyle C_6H_5}{\overset{\displaystyle |}{C}}}H-COOC_2H_5$$

The rotation of the reaction product was —0.09° on dextrorotatory quartz and +0.09° on levorotatory quartz.

All the reactions so far described are conducted under such conditions (starting materials, temperature, catalyst) that it is impossible to visualize their occurrence in nature, without the conditions created by man in the laboratory. The situation is different with the asymmetric cyanoethylation reaction which proceeds at room temperature under the influence of an alkaline catalyst supported on quartz. For example:




In 1953, Ponomarev and Zelenkova carried out asymmetric catalysis using a quartz catalyst in order to demonstrate the possibility of preparing a spiran compound in an optically active form, in which asymmetry is created by the rings themselves and not by the substituents (an optically active alcohol of the tertahydrofuran series is also formed simultaneously):




All asymmetric syntheses over quartz catalysts are characterized by an insignificant optical purity of the reaction products obtained, for which reason this method is of no practical value at present. But it is very impor-

tant from the standpoint of theory: it is one of the plausible mechanisms of creation of "primary asymmetry" in nature (for more detail, see page 638). The results of the asymmetric synthesis on quartz are disputed in the literature (154).

## 2.19. ABSOLUTE ASYMMETRIC PHOTOCHEMICAL SYNTHESIS

In 1860, it was first suggested by Pasteur that there must exist in nature asymmetric physical factors which may induce the formation of optically active substances. The first attempts to find these factors and to use them for asymmetric synthesis were purely empirical and had no success.

In 1894, Pierre Curie pointed out that the role of asymmetric physical agents can be played by circularly polarized light and also light radiation that spreads in parallel to the force lines of a magnetic field. At about the same time Cotton described an effect which is now known as the Cotton effect: it was of decisive importance for carrying out the absolute asymmetric photochemical synthesis.

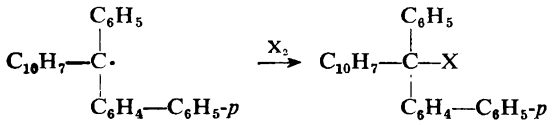
A specific feature of the Cotton effect, which is especially important to the understanding of the essence of photochemical asymmetric synthesis, is that in the region of optically active absorption bands there is observed a phenomenon called **circular dichroism** — the unequal absorption of right- and left-circularly polarized light by enantiomorphs (optical antipodes). One of the antipodes absorbs one component of circularly polarized light more strongly, and the other component is absorbed more strongly by the second antipode. Thus, if a racemate is illuminated with right- or left-circularly polarized light, then one of the antipodes will absorb more light energy than the other, and since it is precisely the absorbed light that can induce chemical changes according to the basic law of photochemistry, the phenomenon described makes it possible to accomplish asymmetric syntheses under the influence of circularly polarized light.

The first attempts to effect asymmetric photochemical synthesis were not successful. The first successful synthesis of this kind was performed in 1929 by W. Kuhn and Braun (155). They claimed to have obtained ethyl α-bromopropionate possessing circular dichroism in the ultraviolet region of the spectrum ($\lambda_{max}$ = 245 nm). By irradiating this ester with circularly polarized light of wavelength 280 nm, Kuhn and Braun found that the undecomposed ester had a small rotation (up to 0.05°). A stronger effect was achieved in an analogous experiment with the dimethylamide of azidopropionic acid. Here the value of circular dichroism at 290 nm is 2-3 per cent; the optical rotation of the undecomposed product is up to 1.04°. Despite the small angles of rotation, there is no doubt that the optical activity appeared as the result of the action of

circularly polarized light and not under the influence of some chance factors. This is proved by the fact that the reversal of the sign of polarization of the light used was followed by the reversal of the sign of rotation of the undecomposed product. Hence, the works of Kuhn and Braun proved the possibility of effecting absolute asymmetric decomposition by means of circularly polarized light.

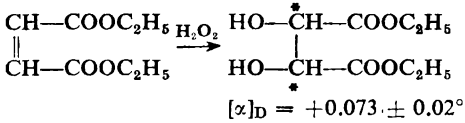
Similar results have been obtained in the preparation of optically active compounds by the action of circularly polarized light on humulene nitrosite, the derivatives of γ-phenylpyridine, and on complexes of chromium with oxalic acid (156).

A truly *synthetic* process induced by the action of circularly polarized light was effected in 1933 by Karagounis and Drykos. They accomplished, under these conditions, the addition of a halogen to the triarylmethyl radical and obtained a product having a rotation of up to ±0.2°:



When bromine was added to trinitrostilbene in a polarized light of wavelength 360-450 nm, a dibromide was formed, which had a rotation of up to 0.04°; an optically active product has also been obtained by the action of chlorine under the analogous conditions.

Tartaric acid, a compound which played a very important part in the development of stereochemistry, has also been produced by absolute asymmetric synthesis. This asymmetric synthesis was effected by the hydroxylation of diethyl fumarate with hydrogen peroxide under the influence of right-circularly polarized light of wavelength 253 nm:

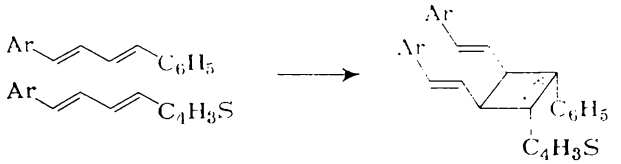


Later, it was reported (157) that all attempts to reproduce this synthesis had failed and in this connection there were raised doubts as to the possibility of carrying out true synthetic (and not destructive) processes under the influence of circularly polarized light.

In the synthesis of helicene structures by the action of circularly polarized light (158), despite a low optical yield (about 0.2 per cent), the observed rotations amounted to almost 10° since the specific rotations of helicenes are very high.

An interesting work was published in 1973 (159), which described the formation of an optically active photodimer under the influence of

*non-polarized light*: the reaction is conducted in a crystal and the asymmetrizing effect is exerted by the chiral packing of molecules in the crystal ($C_4H_3S$ = thiophen residue in the scheme given below):

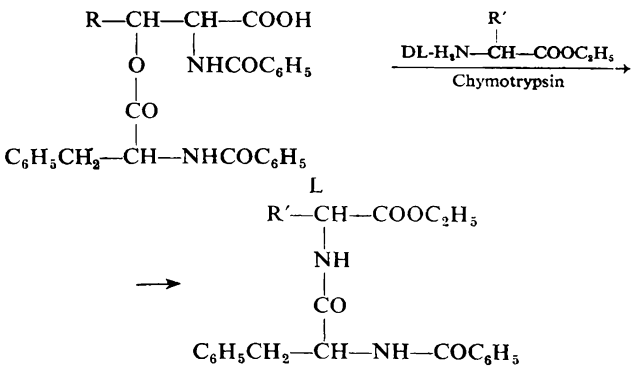


Works on asymmetric synthesis are of fundamental importance in connection with the problem of development of the first optically active organic substances in nature (see page 637).

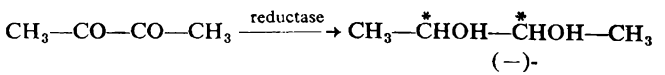
## 2.20. ENZYMATIC ASYMMETRIC SYNTHESIS

The most important feature of enzymatic asymmetric syntheses is their high stereospecificity, which we have repeatedly pointed out in a comparison with ordinary "chemical" asymmetric syntheses.

When the enzyme chymotrypsin acts on racemic esters formed by hydroxy and amino acids, the asymmetric synthesis of peptides proceeds according to the scheme (160):

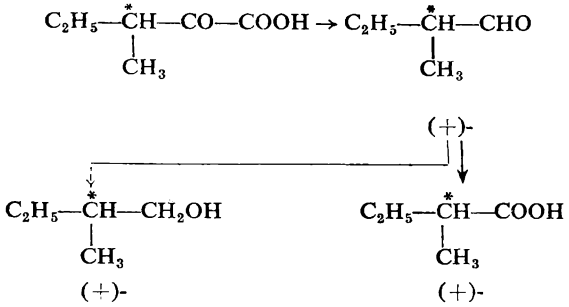


The enzymes isolated from the cells, reductases, are capable of effecting the asymmetric reduction of ketones:



$$C_6H_5—CO—CH_3 \xrightarrow{\text{reductase}} C_6H_5—\overset{*}{C}HOH—CH_3$$
(−)-

Under the influence of the enzymes contained in the yeast juice the racemic methylethylpyruvic acid forms optically active products:



The enzyme isolated from the muscle tissue or from the liver is capable of catalysing the Cannizzaro asymmetric intramolecular reaction:

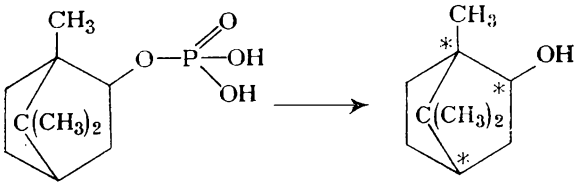
$$CH_3—CO—CHO \rightarrow CH_3—\overset{*}{C}HOH—COOH$$

In this way it is possible to prepare optically active pure (—)-lactic acid.

When acetol is reduced by the action of yeast enzymes, (—)-propylene glycol is obtained, which has an optical purity of the order of 80 per cent:

$$CH_3—CO—CH_2OH \rightarrow CH_3—\overset{*}{C}HOH—CH_2OH$$

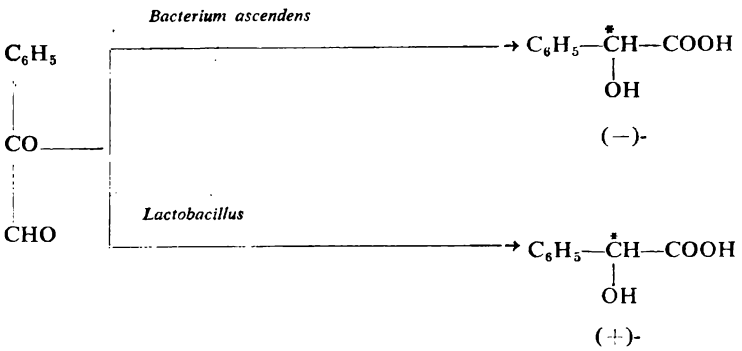
The enzyme phosphatase isolated from the plant or animal tissue can induce the asymmetric hydrolysis of phosphate esters, say, of borneol phosphate:




Racemic

(−)-
Optical purity 25%

Phenylglyoxal is an example of a compound which under the influence of various enzymes can form either the (+)- or (—)-antipode of mandelic acid:




Many other examples of enzymatic (enzymic) asymmetric synthesis could be cited. These examples indicate the route by which asymmetry is reproduced and propagated in living organisms. There have been made the first successful attempts to use stereospecific catalysts, enzymes, for reproducing asymmetric syntheses under laboratory conditions; for this purpose, use is made of immobilized (fixed on a polymeric support) enzymes (161). At the same time, enzymatic asymmetric synthesis does not provide an answer to the question: How was the first optically active organic compound formed on Earth?

* * *

A large number of reviews and books have been published, which are devoted to asymmetric synthesis (162). Extensive material is given in the monograph of Mosher and Morrison (163).

## 2.21. METHODS OF DETERMINATION OF OPTICAL PURITY

After an optically active substance is obtained by the resolution of a racemate or by asymmetric synthesis there invariably arises the question whether it is optically pure, i.e., whether it consists of one enantiomer or contains an impurity of the other as well. The rotation values of optically pure substances may be compared in those cases when a relationship is to be established between the rotatory power of the molecule and its chemical constitution. Changes in the optical purity of a compound during the course of the reactions can provide important information

on their mechanism. In estimating the physiological effect of antipodes, the true ratio of their activities can be obtained only in work with optically pure substances. Finally, in carrying out resolutions it is simply necessary to know whether a given resolution has gone to completion, i.e., whether the enantiomer obtained is really 100% optically pure, or it is only partial, i.e., an incompletely resolved material is obtained.

A crystalline enantiomer is often considered 100% optically pure if its optical rotation and melting point are unchanged by further recrystallization. This criterion, however, cannot be considered to be absolutely reliable: even a partially resolved enantiomer may not change its rotation and melting point if the racemic modification forms a solid solution whose composition is not altered by further crystallization (just as there exist azeotropic mixtures which do not change their composition on distillation). Another criterion is the invariability of the same constants for diastereomeric salts during their additional recrystallization. But this criterion is not absolutely reliable either. A rather satisfactory criterion of absolute optical purity is the fact that *both* enantiomers are obtained with equal rotations (in absolute value), especially when both were resolved in independent fashion, through the use of different asymmetric reagents.

The **enzymatic method** of determination of optical purity is based on the use of the high stereospecificity of enzymes. For example, the enzyme that oxidizes amino acids, the oxidase of amino acids, exhibits high stereospecificity: L-amino acids are oxidized by this enzyme 1000 times faster than D-amino acids. Thus, if we are dealing with a D-amino acid whose optical purity is to be established, the absence of reaction with the amino-acid oxidase will indicate its practically absolute optical purity (not less than 99.9 per cent). If the enzymatic oxidation of the supposedly pure D-amino acid proceeds at a perceptible velocity, this will be an indication that it contains an impurity of an L-amino acid.

The method of double resolution proposed by Horeau is based on the following reasoning. When a racemate consisting of an equimolecular mixture of (+)-A and (—)-A reacts with an optically active substance (+)-B, two reactions actually take place:

$$(+)\text{-A} + (+)\text{-B} \xrightarrow{k_1} \overset{(+)}{\text{A}}\ \overset{(+)}{\text{B}}$$

$$(-)\text{-A} + (+)\text{-B} \xrightarrow{k_2} \overset{(-)}{\text{A}}\ \overset{(+)}{\text{B}}$$

These reactions involve the formation of a pair of diastereomers, and the reactions themselves proceed at different velocities, $k_1 \neq k_2$. If the optically active reagent (+)-B is taken in an insufficient amount, then

after the reaction is complete the enantiomers (+)-A and (—)-A will remain in unequal amounts, i.e., a partial kinetic resolution of the racemate will occur. The change of the rotation may be tied up with the optical purity of substance A if its optical purity is unknown, i.e., if it consists of a mixture of the racemate and one of the antipodes.

In practice, when optical purity is to be determined by this method, two reactions are conducted: the *racemate* (+)-A·(—)-A is brought into reaction with an optically pure reagent (+)-B; in the second reaction the racemate (+)-B·(—)-B is allowed to react with an insufficient amount of an optically active substance A, whose optical purity is to be determined. The rotation of the optically pure substance A is calculated from a formula which contains the following quantities: $[\alpha_A]$ = sought-for specific rotation of the optically pure compound A; $[\alpha_B]$ = specific rotation of the optically pure reagent B; $[\alpha_{A_1}]$ = specific rotation of the unreacted material A in the first reaction; $[\alpha_{A_2}]$ = specific rotation of A used in the second reaction; $[\alpha_{B_2}]$ = specific rotation of the unreacted B in the second reaction:

$$[\alpha_A[ = \sqrt{\frac{[\alpha_{A_1}] \cdot [\alpha_{A_2}] \cdot [\alpha_B]}{[\alpha_{B_2}]}}$$

This formula may be used provided that the yields and the ratios of the reagents in both reactions are the same and the reagent B is 100% optically pure. The calculation can be made also in a more general case when these conditions are not satisfied, but the formula will be more complicated.

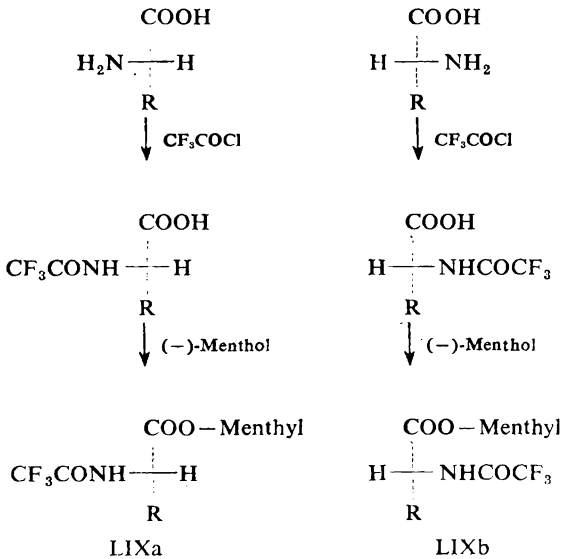
This method has so far been applied most often to the determination of the optical purity of alcohols and amines, α-phenylbutyric anhydride being used as the optically active reagent B. To test the method, optically pure phenyl-*n*-propylcarbinol has been shown by calculation to have a rotation of 29.6° (the experimental value is 29.3°) and benzylethylamine, a rotation of 35.3° (the experimental value is 35.6°).

Optical purity can also be determined by the method of separation by means of gas-liquid chromatography. A substance whose optical purity is to be determined is converted by the action of an optically pure reagent into a derivative which will contain two chiral centres. If the substance was optically pure, one diastereomer would be obtained, but if it contained an impurity of the second antipode, two diastereomers would be produced. In gas-liquid chromatography, the diastereomers can give two separate peaks; the ratio of the areas of these peaks will indicate the ratio of the antipodes in the optically active substance tested for optical purity. Before this method is used it is necessary to make certain, using a substance known to be optically impure, that the diaste-

reomers do indeed emerge from the gas-liquid chromatographic column at different times.

One example of the application of this method is the determination of the optical purity of phenyl-*n*-butylcarbinol carried out by Horeau (164). The rotation value reported in the literature for this compound is $[\alpha]_D^{24} = +17.2°$. Having obtained the ester of this alcohol with (+)-α-phenylbutyric acid, Horeau made certain that two diastereomers had been formed. The ratio of their peak areas enabled him to calculate the optical purity of the alcohol used: the optically pure preparation must have a rotation of $[\alpha]_D^{20} = 20.0 \pm 0.2°$ (without solvent). Another example is the determination of the optical purity of methyl-*o*-fluorophenylcarbinol after it is converted into an ester with methylphenylacetic acid (165).

This method is extensively used to determine the optical purity of amino acids. For this to be done, amino acids were converted into N-trifluoroacetyl derivatives, from which esters were then obtained with (—)-menthol:



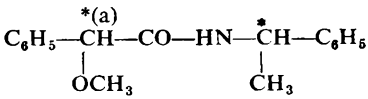

LIXa LIXb

The resulting diastereomers, LIXa and LIXb, will give two peaks on chromatograms if the original optically active amino acid was not absolutely optically pure.

Whether one or two diastereomers have been formed in the reaction with an optically pure substance can also be established with the aid of the **nuclear magnetic resonance method.** In diastereomers the hydrogen

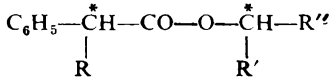
atoms become diastereotopic and therefore the signals of the identical protons in the two diastereomers will be different. Thus, if the test compound contained an antipode as an impurity, then the signals will be found to be duplicated. The ratio of the integral intensities of a pair of signals may be used to determine the ratio of the diastereomers and, hence, the optical purity of the original compound.

Let us consider, as an example, the determination of the optical purity of partially resolved (+)-α-phenylethylamine which has $[\alpha]_D = +22.6°$ (plus 8.6 in methanol). The reagent used was the acid chloride of optically pure *O*-methylmandelic acid. The resulting amide



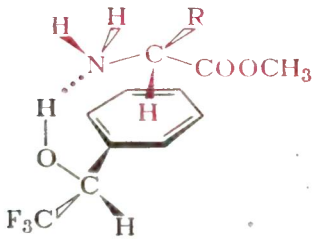

gives an NMR spectrum with two singlets belonging to the protons of the methine group (a), two singlets of the protons of the methoxy group (b) and two C-methyl doublets (c). The ratio of the antipodes in the original α-phenylethylamine was determined from the ratio of the integral peak intensities. It is equal to 90:10, which enabled the optical purity to be calculated (80 per cent) and the rotation of optically pure α-phenylethylamine was determined therefrom. The value found, $[\alpha]_D = +28.3°$ (in methanol), agrees well with the known value, $[\alpha]_D = +28.5°$.

The optical purity of both acids and alcohols can be determined by the use of the NMR spectra of the diastereomeric esters of α-substituted phenylacetic acids with secondary alcohols (166):

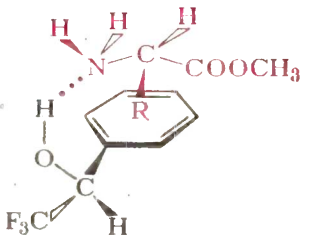



Another example of the application of the NMR method for optical purity determinations is based on the use of optically active solvents: the enantiotopic atoms present in optical antipodes give different chemical shifts in such solvents (167). This method has been employed for the determination of the optical purity of 2,2,2-trifluoro-1-phenylethanol, using (+)-α-phenylethylamine as the solvent, and of amines and the methyl esters of α-amino acids with (—)-2,2,2-trifluoro-1-phenylethanol used as the solvent (168). The differences in the chemical shifts are associated with the formation of diastereomeric solvates. In the case of the interaction of enantiomeric methyl esters of α-amino acids with 2,2,2-tri-

fluoro-1-phenylethanol, the structure of such diastereomeric solvates may be depicted as follows:



LX

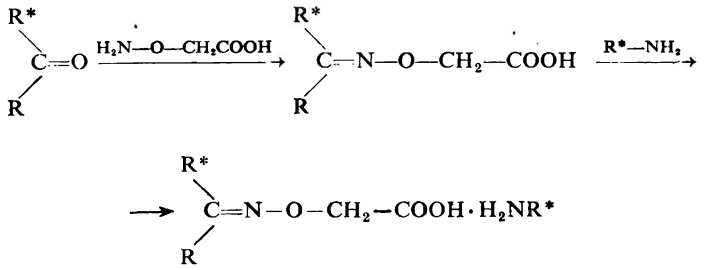


LXI

Their existence is provided by the interaction of the hydroxyl hydrogen with the nitrogen of the amino group and of the π-electron cloud of the benzene ring with the carboxyl carbon atom bearing a partial positive charge. The conditions of formation of solvate LX are more favourable than those for solvate LXI since in the second case the interaction of the ring with the carboxyl carbon is interfered with by the radical of the amino acid, which is turned towards the ring.

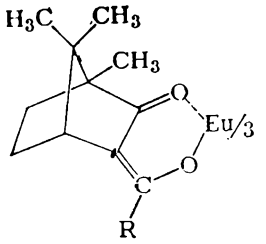
An analogous method has been employed for determining the optical purity of amines (169).

The following procedure has been suggested for determination of the optical purity of ketones containing an asymmetric carbon atom: ketones are allowed to react with *O*-carboxymethylhydroxylamine and then the NMR spectra of the diastereomeric salts of the resulting derivatives with optically active amines are examined (170):



The differences in the chemical shifts of the signals of diastereotopic protons are not great and this hinders the application of the method in question. To increase this difference, the use of optically active shift reagents has been suggested (171), say, the europium complex of *tert*-

butylhydroxymethylidenecamphor LXII [R = $C(CH_3)_3$] and an analogous complex of trifluoromethylhydroxymethylidenecamphor LXII (R = $CF_3$) (172):




LXII

In the presence of these reagents the methine proton of α-phenylethylamine gives a signal in the region of 17 ppm with a difference of about 0.5 ppm for the R- and S-antipodes. An effective separation of the NMR spectra of the antipodes is also observed on dissolution in optically active liquid crystals (e.g., in cholesteryl chloride) (173). For a discussion of the problem of the non-equivalence of the NMR spectra of enantiomers in chiral solvents, the reader is referred to the literature (174).

The **isotope dilution method** is based on the following considerations. Let us prepare a solution containing a racemate labelled with a radioactive or stable isotope and add to it the half weighed amount of one of the optical antipodes (e.g., the dextrorotatory one) of the same substance containing no labelled atom. The solution will thus contain equal amounts of the labelled (—)-antipode, the labelled (+)-antipode, and the unlabelled (+)-antipode. If now the racemate is separated from the solution, then only half of the molecules of the (+)-antipode contained in it will be found to be labelled. This means that the racemate will contain, on the whole, only 3/4 of labelled molecules as compared with the original number. If the unlabelled (+)-antipode added was optically impure, i.e., contained an impurity of the (—)-antipode (or, what is the same thing, an impurity of the racemate), then the fraction of labelled molecules in the recovered racemate will be less than 3/4. Extending this reasoning to a general case, where not a racemate is regenerated but an optically active compound with a rotation (i.e., optical purity) different from that of the antipode added, one can, after the appropriate mathematical computations, arrive at the following formula to be used for calculating the maximum rotation:

$$[\alpha]_{max} = \sqrt{\frac{S_i n^2 [\alpha]^2 - S_0 \overline{mn\,[\alpha]\,[\alpha_i]}}{S_i(m+n)^2 - S_0 m(m+n)}}$$

where $n$ = mass of the antipode being tested for purity (in grams); $m$ = mass of the labelled racemate added; $S_0$ = specific radioactivity of the added labelled racemate; $S_i$ = specific radioactivity of the recovered antipode; $[\alpha]$ = specific rotation of the antipode tested for purity; $[\alpha_i]$ = specific rotation of the recovered antipode. If stable isotopes are used, the values of specific radioactivities are replaced with the contents of isotopic atoms.

Other methods have also been proposed for determination of optical purity, which are based on the differences between the antipodes or their diastereomers, which are determined by means of differential microcalorimetry or circular polarization of luminescence (175). Information on methods of determining optical purity can also be found in the work of Mislow and Raban (176).

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CHAPTER 3

# Determination of Spatial Configuration

As has already been pointed out (see page 63), there is a strict distinction between the *designation* of configuration and its *determination.* In the first case, we deal with conventional techniques allowing us to express, in the names of compounds, the specific features of their spatial structure; in the second, the *experimental verification* of the spatial structure is meant. Only when the configuration of a compound has been determined experimentally is it possible to express the three-dimensional structure by means of a certain model or a corresponding conventional formula and then to give a name to this model or formula.

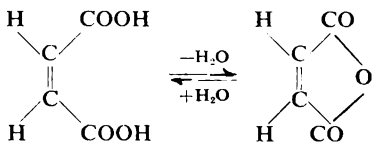
## 3.1. DETERMINATION OF THE CONFIGURATION OF GEOMETRICAL ISOMERS

To illustrate the logic of reasoning in determining the configuration of geometrical isomers, we shall make use of a simple example well known from the general course of organic chemistry. Let us imagine that we are the investigators who have found that there exist two isomeric compounds having the composition $C_4H_4O_4$, called fumaric and maleic acids. Each of these compounds has its own specific properties: maleic acid has a melting point of 130°C, is well soluble in water, and is toxic; fumaric acid melts at 287°C, is relatively slightly soluble in water, is not toxic and occurs in plants. These properties by themselves conveyed to the

investigators no information either on the nature of isomerism or on the structure of the isomers; the properties here serve only as the specific features of the compounds, which allow them to be differentiated from each other.

The first task to be tackled by the investigator who is interested in *why* the two compounds are different from each other may be formulated as follows: What is the nature of the isomerism observed? An answer in this case is provided by experimental evidence that fumaric and maleic acids have the same chemical constitution. This is evidenced by their properties, such as the ability to form salts with two equivalents of univalent ions of metals (this proves that the two acids are dibasic, i.e., that they contain two carboxyl groups), the ability to add a bromine molecule (a proof for the presence of a carbon-carbon double bond), and the ability to be converted on hydroxylation into tartaric acid. These and other chemical transformations indicate that both acids may be represented by the same structural formula: HOOC—CH=CH—COOH. On the other hand, it is known that substituted ethylenes of the type RR′C=CRR″ are capable of existence as two spatial isomers called *cis*- and *trans*-forms. Thus, we have good grounds to regard fumaric and maleic acids as *cis-trans* isomers. The task of determining the configuration thus boils down to finding out which of the acids has a *cis*- and which a *trans*-configuration.

The problem was solved in this particular case by one of the most spectacular and reliable ways—the **method of cyclization.** Maleic acid rather readily loses water on gentle heating and is converted into a cyclic anhydride. Maleic anhydride can add on water even at room temperature, being transformed back into maleic acid. In the cyclic anhydride, the carboxyl-group residues must be in the *cis*-position; such an arrangement is naturally supposed to exist in the acid from which the cyclic anhydride is readily formed and into which it is converted. The method of cyclization allows one to arrive at the conclusion that maleic acid is the *cis*-isomer:

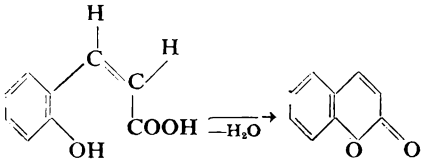



The second isomer, i.e., fumaric acid, has thus the *trans*-configuration.

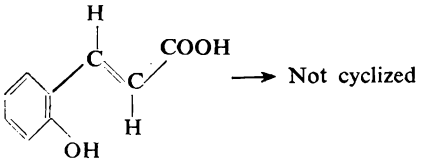
Note an important feature of the reaction leading to the formation of the cyclic anhydride: during the cyclizing process the bonds between the unsaturated carbon atoms and their nearest substituents remain intact. This feature is often expressed as follows: the reaction proceeds with the steric centre remaining untouched. It should be remembered that it is

precisely such reactions that are primarily suitable for configuration determinations. But if the steric centre is disturbed, there appears the possibility of spatial rearrangements and the result of configuration determination may be found to be erroneous if there are no reliable data on the mechanism of the reaction and on its stereochemical result.

Another example of the application of the cyclizing process is the determination of the configuration of a pair of geometrically isomeric hydroxy acids, coumaric and coumarinic acids. The latter exists only in the form of salts and esters; when the free acid is being liberated, it spontaneously forms the lactone, coumarin. The ease of cyclization points to the *cis*-configuration of coumarinic acid:

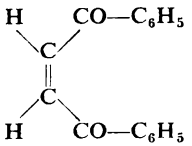



Coumarinic acid Coumarin



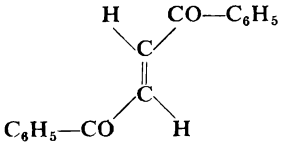

Coumaric acid

The method of cyclization has also enabled the configurations of two ethylene diketones, I and II, to be determined:



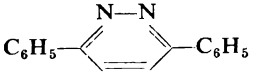

*cis*-1,2-Dibenzoylethylene

I




*trans*-1,2-Dibenzoylethylene

II

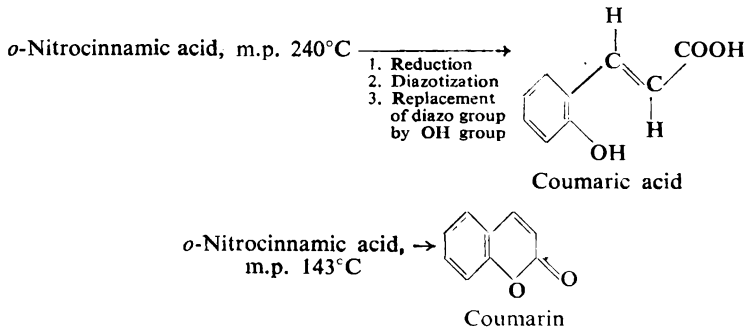



III

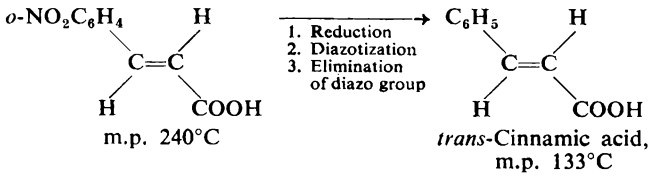
The configuration in this case was determined on the basis of the fact that one of the isomers, namely the *cis*-isomer, more readily gives with hydrazine a cyclic product, diphenylpyridazine III. Certain conclusions

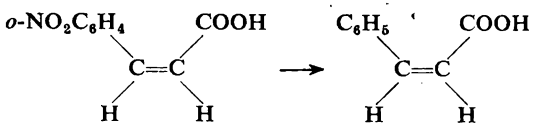
can also be made on the basis of the different colourations of the two isomers: the *trans*-form is deep yellow, while the *cis*-form is colourless. This is accounted for by the fact that the molecule of the *trans*-form is planar, with the undisturbed conjugation between the carbonyl groups, the ethylene linkage, and the aromatic rings: the delocalization of the mobile π-electrons over the conjugated system reduces their excitation energy, which is what leads to the absorption in the visible region of the spectrum. In the *cis*-form, the phenyl rings cannot arrange themselves in one plane because of steric hindrances. The non-planar structure causes a partial break in of conjugation, as a result of which the absorption shifts to the ultraviolet region of the spectrum and the visible colouration disappears.

The second important method of determining the configuration is the chemical transformation of a compound of unknown configuration into a compound the configuration of which is known. Naturally, the steric centre must be left intact in this case too. For example, *o*-nitrocinnamic acid can be converted via *o*-aminocinnamic and *o*-diazocinnamic acids into *o*-hydroxycinnamic acid. Having established which of the stereoisomers of *o*-nitrocinnamic acid gives coumaric acid and which of them coumarinic acid (i.e., in actual fact, the lactone of coumarinic acid), one can thereby find out which of the *o*-nitrocinnamic acids has the *trans*- and which the *cis*-configuration.



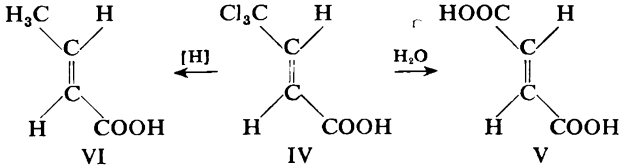

The stereoisomeric *o*-nitrocinnamic acids in their turn are used to determine the configuration of unsubstituted cinnamic acids according to the scheme:





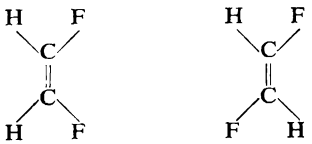

Let us cite an example which points to the necessity to be careful in using chemical conversions for elucidation of the *cis-trans* configuration of compounds. The point is that not infrequently chemical transformations, which formally proceed as ordinary substitution reactions not affecting the steric centre (in particular, the double bond), are in fact accomplished by way of consecutive addition and elimination reactions.

Thus, in the literature there is often cited a classical proof of the configuration of crotonic acid by way of its comparison with fumaric acid. This comparison made by Auwers is based on the conversion of trichlorocrotonic acid IV into fumaric acid V on hydrolysis and into crotonic acid VI on reduction:




At first glance it seems that the double bond remains intact in these conversions and, hence, the reactions given can safely be used for determination of the configuration. However, as has been shown by A. N. Nesmeyanov and his coworkers (1), the evidence obtained by Auwers is in fact invalid (though, by mere chance, it does provide the correct answer!). The point is that the two-stage conversion of trichlorocrotonic into crotonic acid according to the Auwers scheme involves a double rearrangement which affects the double bond.

Apart from chemical methods of determining the *cis-trans* configuration, use is also made of physical methods. Differences in the symmetry of isomers manifest themselves especially distinctly in the *dipole moments* of compounds. In the case of symmetrically substituted ethylenes, the *trans*-form has no dipole moment and thereby sharply differs from the *cis*-form; for example:



*cis*-1,2-Difluoroethylene, $\mu = 2.4D$



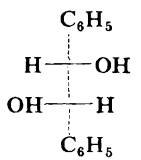
*trans*-1,2-Difluoroethylene, $\mu = 0$

For more complex compounds, both geometrical isomers may have a dipole moment. In such cases, the configuration can be determined by comparing the experimentally found values of dipole moments with those calculated by vectorial addition.

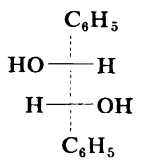
The configuration of geometrical isomers can also be determined by using the data provided by IR, UV, and NMR spectra. Direct information on the geometry of molecules can be obtained by X-ray structural and electron diffraction methods. The spectral differences between *cis*- and *trans*-isomers will be discussed in more detail in Chapter 6.

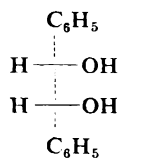
## 3.2. DETERMINATION OF THE CONFIGURATION OF DIASTEREOMERS

Diastereomers, which are compounds with several chiral centres, may differ from one another in symmetry. This provides a reliable method of identifying a racemic diastereomer: of a pair of DL- and *meso*-diastereomers only the first one is capable of being resolved into optical antipodes; the *meso*-isomer is rigidly non-resolvable. Thus, the diastereomer that can be resolved into optical antipodes must be recognized as the DL-form (racemate); the second diastereomer will thus be the *meso*-form. An example is furnished by the determination of the configuration of hydrobenzoin. Having two chiral centres, this compound is capable of existence in the form of two diastereomers; their melting points are 121 and 139°C. The isomer with m.p. 121°C has been resolved into optical antipodes and, hence, it is the DL-diastereomer, which means that the isomer with m.p. 139°C is the *meso*-form:




DL-Form, m.p. 121°C
(isohydrobenzoin)




*meso*-Form, m. p. 139°C
(hydrobenzoin)

If an attempt to obtain one of the diastereomers in an optically active form *has failed*, this does not necessarily mean that it is the *meso*-form; probably, the wrong method of resolution has been chosen (!). In other words, only the *positive* result—the fact that an optically active compound has been prepared—may serve as a basis for configuration assignment.

Compounds with two *different* asymmetric centres exist in the form of two diastereomers, each of which is capable of being resolved into optical antipodes (enantiomers). In such cases, the compound under study can be converted into a compound with two identical chiral centres. If the

centres themselves have remained intact or if the stereochemical course of the conversion taking place at these centres is firmly known, then the formation of the *meso*-form will point to the *erythro*- and that of the DL-form to the *threo*-configuration of the starting compound. This route was chosen by Stefanovsky and Kurtev (2) for the determination of the configuration of 3-amino-2,3-diphenylpropionic acid VII. This acid was prepared by them in the form of two stereoisomeric forms, the configurations of which follow from the following conversions:

$C_6H_5—CH(NH_2)—CH(C_6H_5)—COOH$ $\qquad$ $C_6H_5—CH(NH_2)—CH(NH_2)—C_6H_5$

VII $\qquad$ VIII

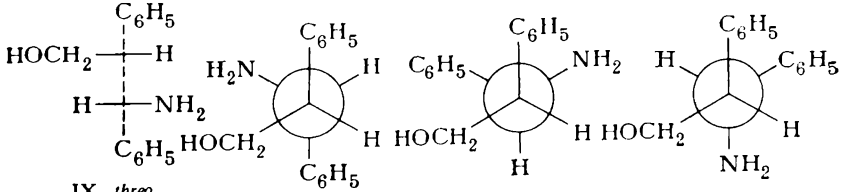
Form with m.p. 174-176°C ⟶ *meso*-stilbenediamine
Form with m.p. 200-201°C ⟶ DL-stilbenediamine

The sequence of chemical reactions used for the conversion of VII into VIII involves the phthalyl protection of the amino group, the conversion of the COOH group into the acid chloride and then into the azide, and the Curtius rearrangement. The last-named reaction affects the asymmetric centre, but it is known to proceed with retention of configuration.

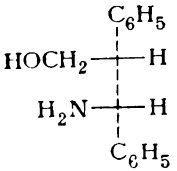
The configurations of the same diastereomeric acids have also been determined by using an indirect method based on the estimation of the ability to form an intramolecular hydrogen bond from the data furnished by IR spectra (3). For this purpose, the diastereomeric amino acids were converted by the action of lithium aluminium hydride into amino alcohols:

$$C_6H_5—CH(NH_2)—CH(C_6H_5)—COOH \xrightarrow{LiAlH_4} \longrightarrow C_6H_5—CH(NH_2)—CH(C_6H_5)—CH_2OH$$

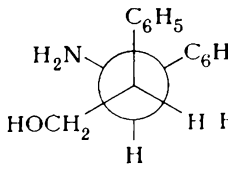
The following conformations can be predicted for diastereomeric amino alcohols IX and X:



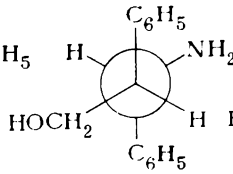

IX, *threo* $\qquad$ IXa $\qquad$ IXb $\qquad$ IXc



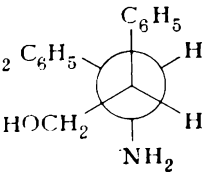

X, *erythro*




Xa




Xb

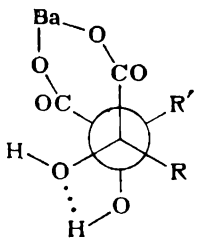



Xc

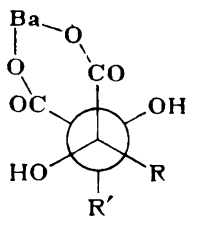
It may be expected that the *threo*-isomer exists exclusively in conformation IXa which is favourable for steric reasons (the bulky $C_6H_5$ groups are far away from each other) and, besides, is stabilized by an intramolecular hydrogen bond formed between the $NH_2$ and OH groups. The *erythro*-isomer may be expected to exist as a combination of conformations Xa and Xb; the first conformation is favoured by the formation of an intramolecular hydrogen bond, and the second one is favourable because of the transoid disposition of the $C_6H_5$ groups.

A study of the IR spectra of the amino alcohols indicated has shown that the diastereomer obtained from an amino acid with m.p. 200-201°C has a more intense band corresponding to the intramolecular hydrogen bond in the region of 3100-3500 $cm^{-1}$. On this basis, the diastereomer in question should be regarded as the *threo*-form and, hence, the amino acid VII with m.p. 200-201°C has the *threo*-configuration.

The differences in the IR spectra of calcium and barium salts have enabled the configuration of alkyltartaric acids to be determined (4): a band corresponding to an intramolecular hydrogen bond appears only in the *erythro*-form XI, while in the *threo*-form XII the OH groups are far apart from each other and no intramolecular hydrogen bond can be formed:



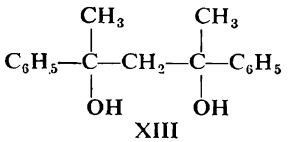

XI




XII

The identification of DL- and *meso*-forms by PMR spectra is based on the fact that in the *meso*-forms of compounds of the R*—$CH_2$—R* type (R* = radical with an asymmetric centre) the protons of the $CH_2$ group are diastereotopic and therefore give two signals, and in the DL-

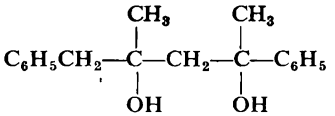
forms they are equivalent and give only one signal. An example is the study of the configuration of diastereomeric glycols XIII (5):



XIII

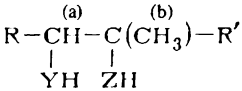
The DL-form (m.p. 106°C) gives one signal from the $CH_2$ group at 2.38 ppm. The *meso*-form (m.p. 117°C) gives two signals of the $CH_2$ group at 2.40 and 2.53 ppm.

Differences in the NMR spectra have also been detected for other stereoisomeric pairs of *meso*- and racemic forms (6). If the diastereomers are unsymmetrical (i.e., *threo*- and *erythro*-forms exist instead of DL- and *meso*-forms), then each of the two diastereomers gives two signals of the $CH_2$ group, but the difference between the two signals is smaller for the *threo*-form; for instance, for XIV:

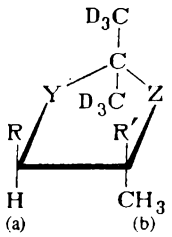


| XIV | $\delta_{CH_2}$ | | $\Delta\delta$ |
|---|---|---|---|
| *threo*- | 2.67 | 2.74 | 0.07 |
| *erythro*- | 2.18 | 2.48 | 0.30 |

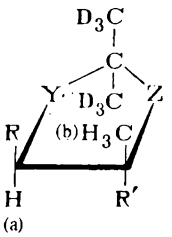
For α-glycols and related compounds, there has been proposed a method for identifying *threo*- and *erythro*-isomers, which is based on the use of double proton magnetic resonance (7). Compounds of the general formula XV are converted by the action of deuteroacetone into cyclic acetals in which the relative disposition of $\overset{(a)}{H}$ and $\overset{(b)}{CH_3}$ depends on the configuration of the starting compounds.



XV (Y and Z = O,S,NR″)



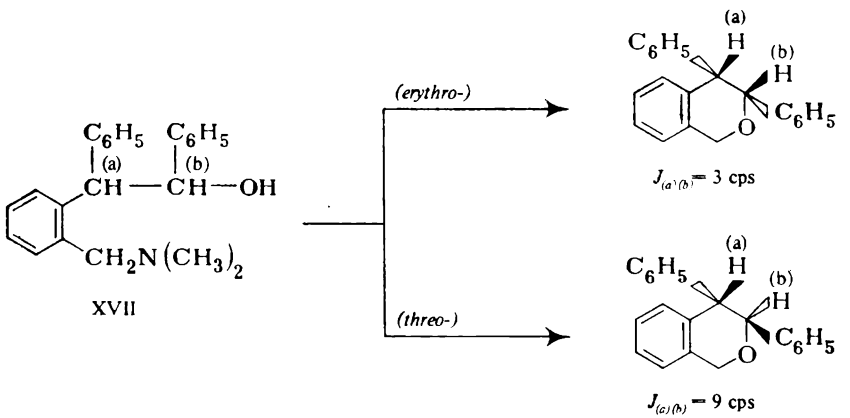
XVIa



XVIb

In the double PMR method, at the frequency of the $CH_3$ group of derivatives of the *erythro*-forms (XVIa) there is observed, across the methine proton $\overset{(a)}{H}$, the nuclear Overhauser effect (NOE), i.e., an increase in the integral intensity of the signal at constant width. The derivatives of *threo*-forms in an analogous experiment show a so-called interaction of the W-type — the integral intensity of the $\overset{(a)}{H}$ signal does not vary: the signal increases in height, but its width diminishes.

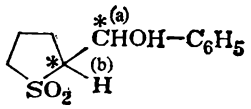
In many cases, for the configuration of diastereomers to be determined, they are converted into cyclic derivatives, as a result of which the conformational mobility is lowered. From *threo*- and *erythro*-forms there are obtained, in such cases, derivatives which differ in the orientation of the substituents relative to the ring. This orientation can be established rather easily by the NMR method, using the following general regularity: the closer are the interacting protons to one another, the lower the spin-spin splitting constants. For instance, the *threo*- and *erythro*-diastereomers of compound XVII give the following stereoisomeric isochromanes when reacted with methyl iodide and then heated:



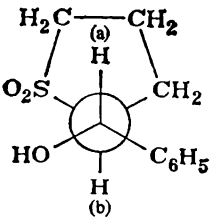

XVII

Their configurations follow from a comparison of the spin-spin splitting constants $J_{(a)(b)}$: with the *erythro*-configuration of the starting compound XVII the closely spaced protons have lower spin-spin splitting constants than the same but remotely spaced protons in the isochromane obtained from the *threo*-isomer (8).

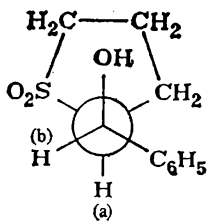
The spin-spin splitting constants have also been used to solve (9) the problem of the configuration of diastereomeric hydroxy sulphones XVIII:



XVIII

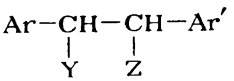


$J_{(a)(b)} = 9.9$ cps
*(threo-)*



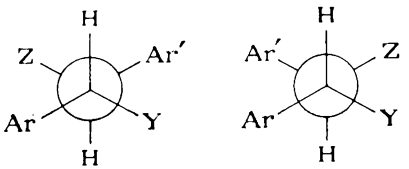
$J_{(a)(b)} = 2.2$ cps
*(erythro-)*

Data on chromatographic mobility may also be used for configuration assignment in the case of diastereomers (10). For example, in a study of a large group of compounds of the XIX type it has been established that the *erythro*-forms are more mobile than the *threo*-forms. The authors of the work cited ascribe this to the preferred conformations: in the *threo*-form, *both* polar groups can interact with the adsorbent surface, and therefore they are more firmly attached to the adsorbent and must be less mobile (see the Newman formula on the right):



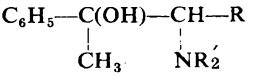
XIX

Y and Z = NHR, OH, COOH, $COOCH_3$ and other polar groups;
Ar and Ar' = $C_6H_5$, *m*- or *p*-$C_6H_4OAlk$



It is interesting that this regularity is obeyed by compounds with and without intramolecular hydrogen bonds: the hydrogen bond is probably broken on adsorption.

For configuration assignment in the case of diastereomeric substituted 3-aminopropanols (11)



use was made of the data of gas-liquid chromatography (along with IR spectral data).

The diastereomeric character is also shown by the *cis-trans* isomers of cyclic compounds: methods of determination of their configuration are similar to those described above. A more detailed account is given in Chapter 5.

## 3.3. DETERMINATION OF THE CONFIGURATION OF OPTICAL ANTIPODES

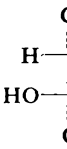
The task of determination of the configurations of optical antipodes (enantiomers) is basically set up in the same way as in the case of *cis-trans* isomers or diastereomers. Here again we have two compounds — the levo- or dextrorotatory antipodes that are to be correlated to two mirror-image tetrahedral models or the corresponding projection formulas.

A certain psychological complication arises because of the left- or right-hand rotation being practically the only feature distinguishing the antipodes from each other. It is tempting to regard the sign of rotation as a direct reflection of the configuration. But, of course, this is not so, as has already been pointed out.

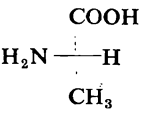
A reliable basis for the determination of the configuration of optically active compounds with an asymmetric carbon atom is furnished by a special X-ray diffraction analysis using a heavy atom introduced into the molecule. In this method, called the heavy-atom method, use is made of X-rays with a wavelength close to the edge of the X-ray absorption of the heavy atom introduced into the molecule as a label. As a result, onto an ordinary diffraction pattern there is superimposed a phase shift and the X-ray diffraction patterns of the optical antipodes become non-identical. For the two decades that have lapsed since the discovery of the X-ray diffraction method of determination of the absolute configuration of compounds, X-ray diffraction studies have been considerably simplified and the time required was much shortened owing to the use of automatic diffractometers and electronic computers.

The X-ray method of determining absolute configuration was first applied to tartaric acid. This was done in 1951 by Bijvoet, Peerdeman and van Bommell in the same laboratory where van't Hoff worked in

the last century. During the time that elapsed since the discovery of the X-ray diffraction method of determining absolute configuration there have been established the configurations of about two hundred optically active compounds, including organic compounds and optically active complexes. For an overview of all these data the reader is referred to the literature (12). Absolute configurations are now known for various hydroxy acids, amino acids, terpenoids, steroids, alkaloids, sugars. For example:



*R,R*-(+)-Tartaric acid



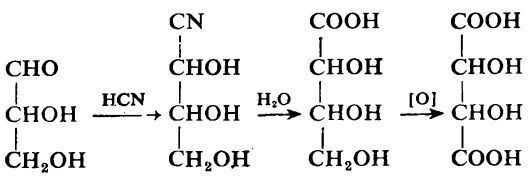
*S*-(+)-Alanine

However, as compared with the total number of known optically active substances, the absolute configuration has been determined for only a relatively limited number of substances. The configurations of most optically active compounds have been elucidated by their *correlation* with other substances of known configuration.

### 3.3.1. CHEMICAL CORRELATION OF CONFIGURATIONS

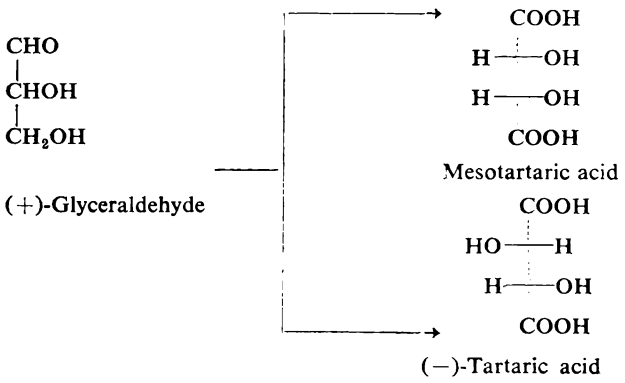
For correlation to be effected by means of chemical reactions two substances are bound with each other, one [for example, (+)-A)] of known and the other (say, X) of unknown configuration. After the conversion is complete, a polarimeter is used to find out which of the antipodes has been formed (let us say, the levorotatory antipode is formed). Considering that the configuration has not changed during the correlation, it is possible to draw a conclusion of the following type: as a result of the chemical conversions used for the correlation, the substance (+)-A is transformed into the levorotatory antipode of substance X; hence, the configurations of (+)-A and (—)-X are identical. Of course, for a correlation to be effected, it is necessary to use only those reactions the stereochemical result of which is known (as a rule, the bonds about the asymmetric centre must remain intact).

Thus, glyceraldehyde can be converted into tartaric acid by building it up by means of cyanohydrin synthesis:

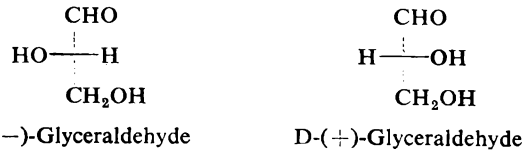


The only asymmetric carbon centre present in glyceraldehyde is left intact and must therefore have the same configuration in tartaric acid as in the parent compound. During the building-up process, a second asymmetric centre (the top one in the formulas) is introduced into the molecule, this centre being in principle formed in the form of both possible configurations.

This transformation was carried out experimentally in 1917 by Wohl and Momber. It was found that from dextrorotatory glyceraldehyde there is obtained levorotatory tartaric acid (along with the mesotartaric acid). Since the absolute configuration of (—)-tartaric acid is known, the stereochemical result may be expressed by the scheme:

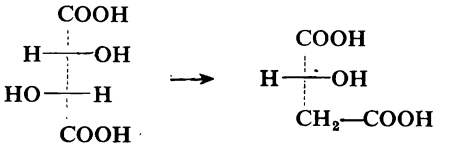



From this it follows that the asymmetric centre in the original (+)-glyceraldehyde must be assigned the same configuration as in (—)-tartaric acid:



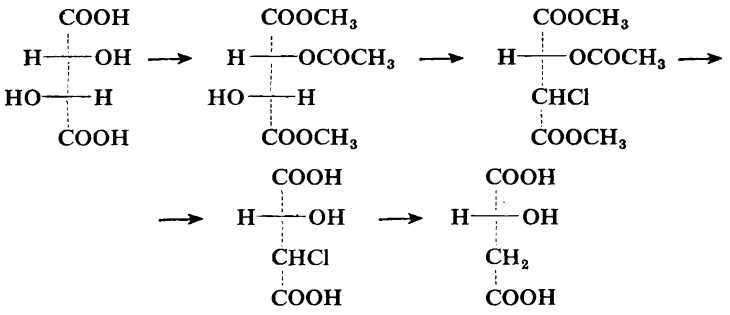

It may seem that we have selected arbitrarily the bottom asymmetric centre of (—)-tartaric acid for deriving the configuration of glyceraldehyde. The result, however, will not change if we choose the top asymmetric centre because both centres here have the same configuration, which is only written differently. On the other hand, in mesotartaric acid the configuration of both centres is opposite and, hence, gives no indication as to the configuration of the original glyceraldehyde.

On reduction with removal of one hydroxyl group (+)-tartaric acid can be transformed into (+)-malic acid, which is what specifies the configuration of the latter:



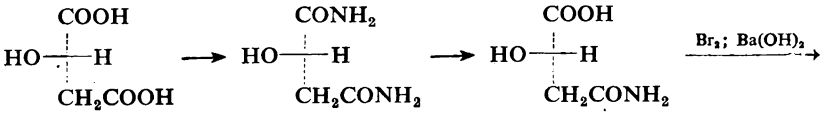
*R,R*-(+)-Tartaric acid *R*-(+)-Malic acid

Such a conversion was first accomplished as early as 1875 by the action of hydrogen iodide. The conclusion made in this way was however considered to be unreliable since the conversion proceeded with a negligibly low yield and under conditions that did not exclude the possibility of the configuration of the asymmetric centre being changed. It was for this reason that several decades later Freudenberg (19, 22) once again took up the problem of correlation of the configurations of tartaric and malic acids. The chemical transformation was this time effected in a different way, but the stereochemical result was the same as before:

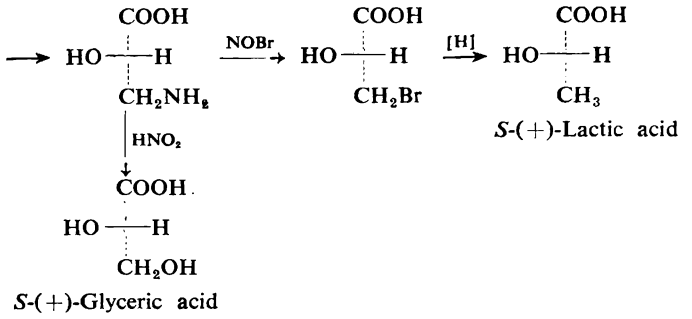


*R*-(+)-Malic acid

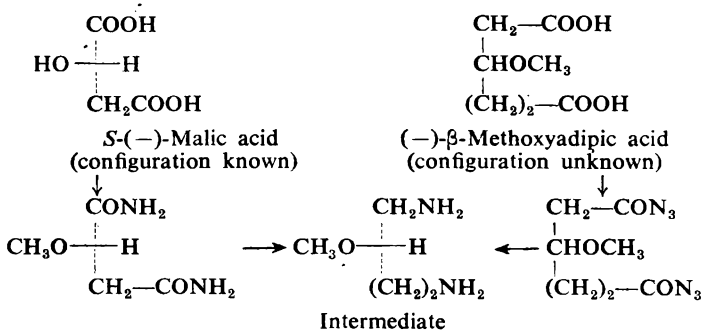
In 1914 Freudenberg correlated natural *S*-(—)-malic acid with two other important hydroxy acids — glyceric and lactic acids. The following chemical changes were used for the purpose:



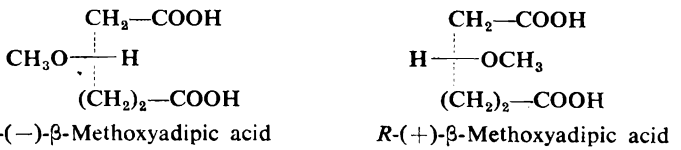
*S*-(—)-Malic acid




The determination of the configuration of β-methoxyadipic acid serves as an example of correlation, in which use was made of two different routes (from a compound of known configuration and from a compound of unknown configuration) to the same intermediate:

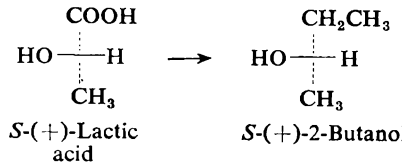



From this it follows that the β-methoxyadipic acids may be represented by the following projection formulas:




Acids of established configuration have been used for correlation with other optically active oxygen-containing compounds. For instance, on the basis of lactic acid there has been determined the configuration

of the simplest optically active alcohol, 2-butanol. The stereochemical result of this correlation may be formulated as follows:

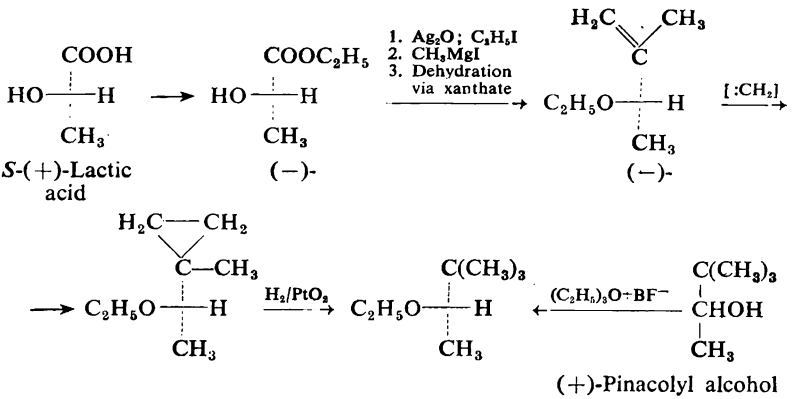



Experimentally the route proved to be rather long: (+)-lactic acid was esterified at the carboxyl group, the ester grouping reduced to the alcoholic group and a series of reactions:

$$—CH_2OH \rightarrow —CH_2Br \rightarrow —CH_2CN \rightarrow —CH_2CH_2NH_2 \rightarrow —CH_2CH_2OH \rightarrow$$
$$\rightarrow —CH_2CH_2I \rightarrow —CH_2CH_3$$

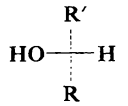
were carried out to convert the COOH group to the ethyl group.

Jacobus *et al.* (13) used lactic acid for elucidating the configuration of a more complex alcohol, 3,3-dimethyl-2-butanol (pinacolyl alcohol):



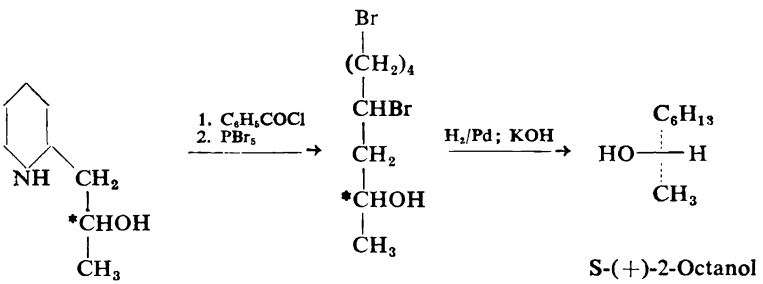

In the course of the correlation the carboxyl group of (+)-lactic acid was eventually converted into a *tert*-butyl group with the formation of the dextrorotatory antipode of pinacolyl alcohol. Now we may write the following projection formulas:

A large number of works devoted to the establishment of the configurations of alcohols have made it possible to arrive at a generalization expressed by the scheme:



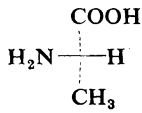
The projection formula represents the (+)-antipode if R′ = large radical and R = small radical

The configuration of 2-octanol has been used to elucidate the configuration of the asymmetric centre in the side chain of the piperidine alkaloid sedridine (14):

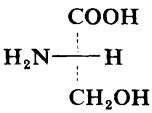



S-(+)-2-Octanol

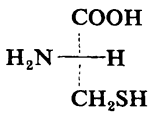
The absolute configuration of natural (dextrorotatory) alanine (see page 181), which has been proved by the X-ray diffraction method, may serve as a reference standard for determination of the configurations of compounds with an amino group attached to the asymmetric carbon atom. For example, in 1907 Emil Fischer effected the replacement of the hydroxyl group of (—)-serine with a chlorine atom by the action of phosphorus pentachloride; the intermediate was then reduced to (+)-alanine which was converted into (—)-cysteine by the action of $Ba(SH)_2$. The following formulas may thus be written for the amino acids mentioned:




L-(+)-Alanine
(*S*-(+)-alanine)

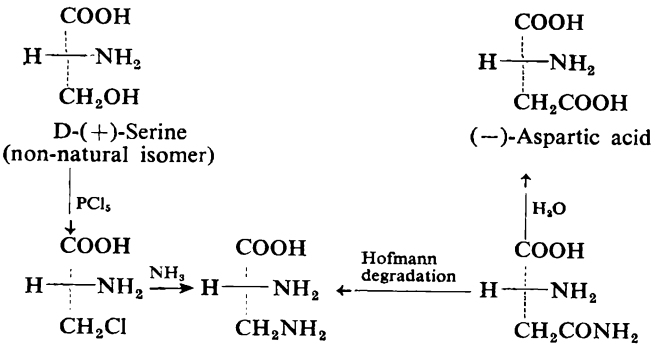



L-(−)-Serine
(*S*-(−)-serine)

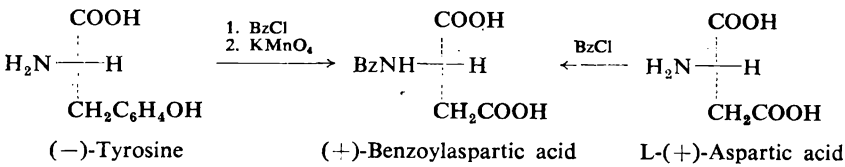



L-(−)-Cysteine
(*R*-(−)-cysteine)

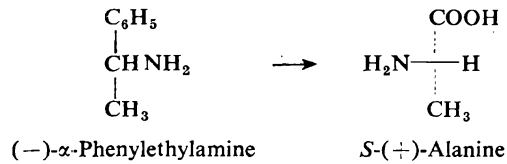
The correlation with serine has allowed the configuration of aspartic acid to be determined:




Aspartic acid in its turn has been used for determination of the configuration of tyrosine (Bz = $COC_6H_5$):

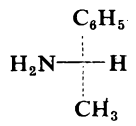



Amino acids have served as a basis for elucidation of the configurations of other, simpler nitrogen-containing compounds — the amines. Thus, a configurational relation was established in 1931 between α-phenylethylamine and alanine due to the works of Leute:

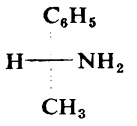



For this transformation to be accomplished, the following reactions were successively carried out: benzoylation, nitration, reduction, diazotization, boiling with water, oxidation with chromic anhydride in acetic acid.

Thus, the configuration of α-phenylethylamine must be represented by the following projection formulas:

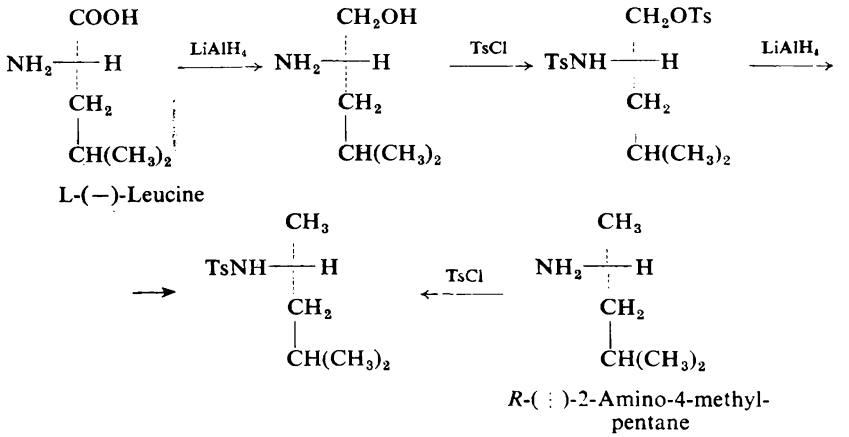


*S*-(−)-α-Phenylethylamine



*R*-(+)-α-Phenylethylamine

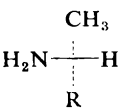
An especially convenient reagent for the elucidation of the configurational relationship between amino acids and amines (and also between hydroxy acids and alcohols) is lithium aluminium hydride. Using this reagent, it is easy to convert amino acids into amines. As an example, let us consider the configuration determination carried out in 1953 by Karrer (Ts = $SO_2C_6H_4CH_3$-*p*):



L-(−)-Leucine

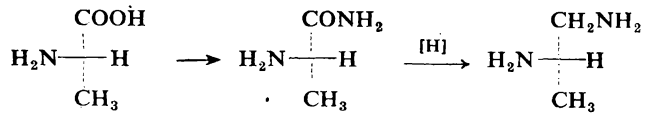
*R*-( : )-2-Amino-4-methylpentane

The rotation of the 2-amino-4-methylpentane used for correlation was measured in Karrer's work in methanol solution. But when Mazur (15) studied the problem of the configuration of this and related compounds, it turned out that with no solvent an amine of *R*-configuration rotates *to the left*. The same sign of rotation is shown in the absence of a solvent by other amines having the *R*-configuration:



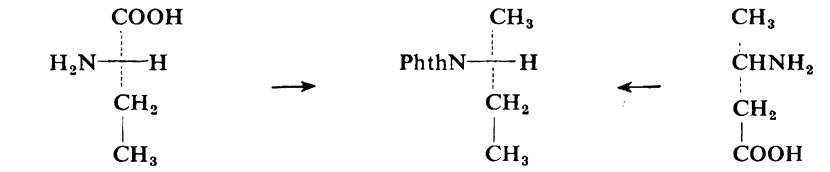
R = *iso*-$C_4H_9$, *iso*-$C_6H_{13}$, cyclohexyl

The conversion of L-(+)-alanine into an amide followed by reduction has enabled determination of the configuration of 1,2-propylenediamine:

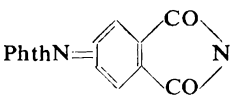


L-(+)-Alanine — *S*-(+)-1,2-Propylenediamine

While the configurational relations of α-amino acids have been studied rather thoroughly, the analogous data for amino acids with a different disposition of the amino group are considerably less complete. The configuration of β-aminobutyric acid has been determined by its conversion to 2-phthalimidobutane, which has also been prepared from α-aminobutyric acid, a compound of known configuration. Omitting the intermediate stages, this correlation may be presented as follows:



*S*-(+)-α-Aminobutyric acid — (−)-2-Phthalimidobutane — (−)-β-Aminobutyric acid

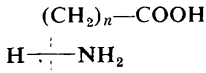


Thus, the configurations of β-aminobutyric acid may be represented by the following projection formulas:

*R*-(−)-β-Aminobutyric acid — *S*-(+)-β-Aminobutyric acid

In its turn, the configuration of β-aminobutyric acid was chosen for determination of the configurations of γ-aminovaleric and δ-amino-

caproic acids (16). It has been shown that the dextrorotatory antipodes of these amino acids have the *R*-configuration:

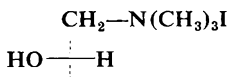


*R*-(+)-Antipodes
$n = 2, 3$

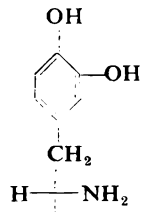
On the basis of the known configurations of amino and hydroxy acids there have been determined the configurations of the amino alcohols, α- and β-methylcholine and α-methyldopamine (17):



*R*-(+)-α-Methylcholine iodide

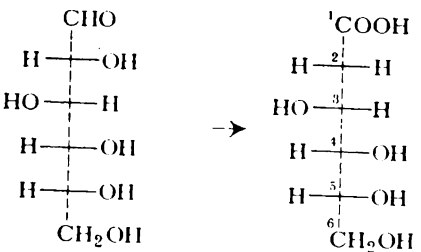


*S*-(+)-β-Methylcholine iodide



*R*-(−)-α-Methyldopamine

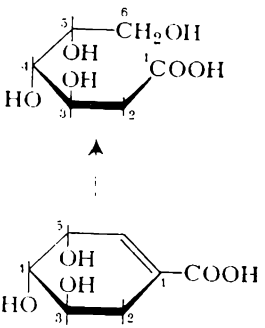
All the compounds considered so far had a *secondary* asymmetric carbon atom of the type R—CHX—R′. But among the naturally occurring optically active compounds there are many important compounds containing a *tertiary* asymmetric carbon atom of the type RR′R″CX. The approach to the determination of the configuration of such compounds was indicated in a series of works by Freudenberg (18). The reference substance used was (—)-shikimic acid isolated from natural compounds; the configuration of shikimic acid is known through its relation to glucose (for the configuration of glucose, see page 606):



D-(+)-Glucose (open form)

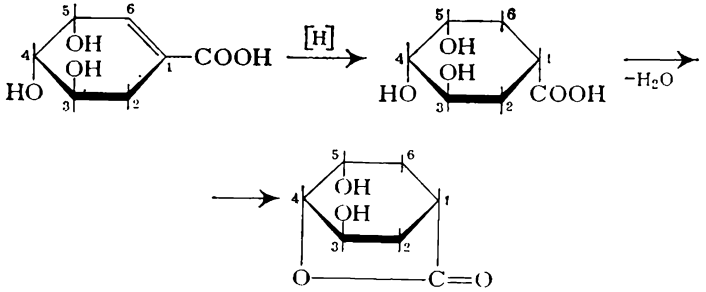
Glucodesonic acid

or written otherwise

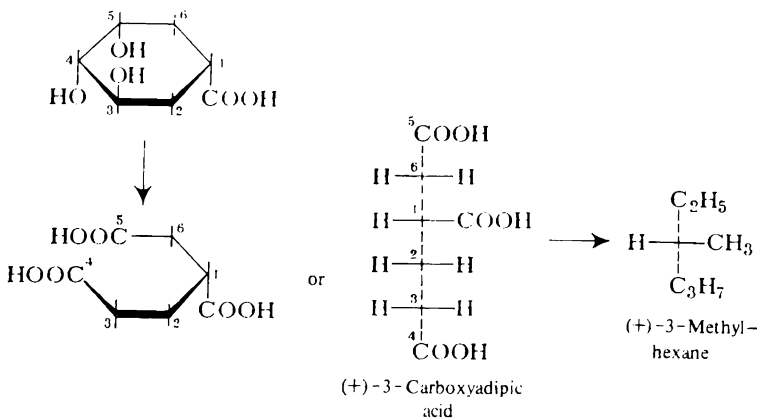


(−)-Shikimic acid

When the double bond is subjected to hydrogenation, (—)-shikimic acid turns into dihydroshikimic acid, the $C_1$ atom becoming asymmetric. The configuration of this new centre is established on the basis of the fact that dihydroshikimic acid is capable of forming a δ-lactone, and this is possible only if the carboxyl group present in the ring is *cis* to the corresponding hydroxyl group:



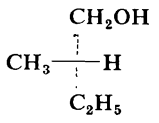

Thus, using the method of cyclization, one can correlate the configuration of the tertiary asymmetric atom $C_1$ with the known configuration of the $C_4$ atom and, hence, there is a reference standard for determining the configuration of related compounds. Dihydroshikimic acid, however, is too complex a compound to be vividly compared with other compounds having a tertiary asymmetric atom. It is for this reason that Freudenberg converted dihydroshikimic acid into 3-carboxyadipic acid and then into 3-methylhexane without disturbing the asymmetric centre:



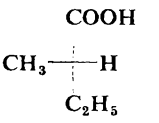

Each of the conversions marked with an arrow required in fact a large number of steps, constant care being taken not to break any of the bonds

to the asymmetric centre; but, in order not to distract the attention from the stereochemical result, we shall not dwell on the details of these transformations.

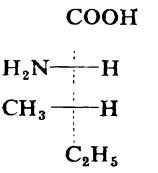
After the configuration of 3-methylhexane had been established it became possible to determine the configurations of many other important substances with a tertiary asymmetric carbon atom without performing new experiments, use being only made of the results of the conversions of optically active substances described earlier. Examples are the following:



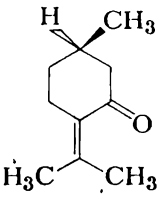
*S*-(−)-2-Methyl-1-butanol
(optically active amyl alcohol)



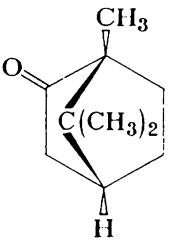
*S*-(+)-2-Methyl-
butyric acid



*S,S*-(+)-Isoleucine

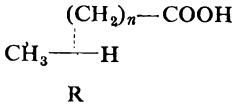


*R*-(+)-Pulegone

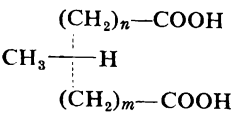


*R,R*-(+)-Camphor

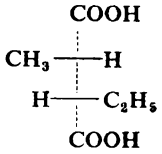
Later, many other works appeared, which were devoted to the determination of the configurations of compounds with a tertiary and a quanternary carbon atom. We shall not discuss the course of these determinations; only some of the results are given below:



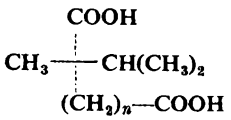
*S*-(+)-4-Methylcaproic acid
(R = $C_2H_5$; $n = 2$)
*S*-(+)-2,3-Dimethylbutanoic acid
[R = $CH(CH_3)_2$; $n = 0$] (19)
*S*-(+)-2,3,3-Trimethylbutanoic acid
[R = $C(CH_3)_3$; $n = 0$] (19)



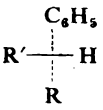
*S*-(−)-2-Methylsuccinic acid
($n = 0$; $m = 1$)
*S*-(+)-2-Methylglutaric acid
($n = 0$; $m = 2$)
*S*-(+)-2-Methyladipic ac
($n = 0$; $m = 3$) (20)
*S*-(−)-3-Methyladipic acid
($n = 1$; $m = 2$) (20)



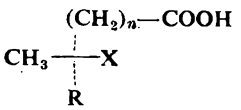
2*S*, 3*S*-(−)-*threo*-2-Methyl-3-ethylsuccinic acid (21)



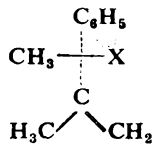
*S*-(+)-2-Methyl-2-isopropylsuccinic acid ($n = 1$) (22, 23)
*S*-(+)-2-Methyl-2-isopropylglutaric acid ($n = 2$)



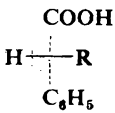
*S*-(−)-3-Methyl-2-phenylbutane [R = $CH(CH_3)_2$; R′ = $CH_3$] (26)
*S*-(−)-2-Methyl-3-phenylpentane [R = $CH(CH_3)_2$; R′ = $C_2H_5$] (27)



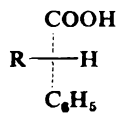
*S*-(−)-2-Cyano-2-methylbutanoic acid (R = $C_2H_5$; X = CN; $n = 0$) (24)
*S*-(−)-2-Hydroxy-2-methyl-3-butyn-1-oic acid (R = C≡CH; X = OH; $n = 0$) (25)
*R*-(−)-3-Cyano-3-methylpentanoic acid (R = $C_2H_5$; X = CN; $n = 1$) (24)



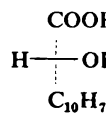
*S*-(+)-2-Methyl-3-phenyl-1-butene (X = H) (26)
*R*-(−)-2-Methyl-3-methoxy-3-phenyl-1-butene (X = $OCH_3$) (28)



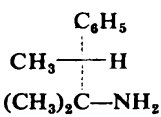
*R*-(−)-2-Phenylalkanoic acids (R = Alk; $n = 0$) (29)



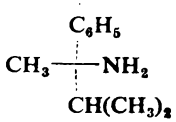
*S*-(+)-2-Benzylphenylacetic acid (R = $CH_2C_6H_5$) (30)
*S*-(+)-2-Isopropylphenylacetic acid [R = $CH(CH_3)_2$] (31)*



*R*-(−)-α-Naphthylglycolic acid (33)

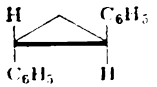


R-(−)-2-Methyl-3-phenyl-2-butylamine (26)



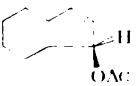
*R*-(−)-3-Methyl-2-phenyl-2-butylamine (26)

* The configuration of 2-isopropylphenylacetic acid given in (32) is incorrect.

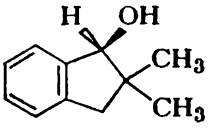


*R,R*-(−)-*trans*-1,2-Diphenyl-cyclopropane (34)

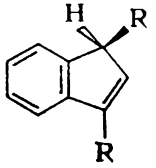
*R*-(+)-Cyclohexene-3-carboxylic acid and (−)-4-alkylcyclo-hexenes (35)



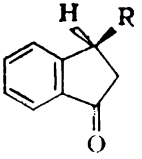
*S*-(+)-3-Acetoxy-cyclononene (36)



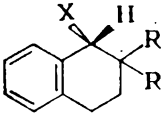
*S*-(+)-2,2-Dimethyl-1-indanol (37)



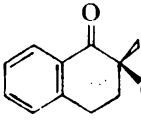
*S*-(+)-1,3-Dialkyl-1-indenes (29)



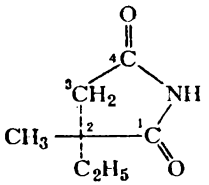
*S*-(+)-3-Alkyl-1-indanones (29)



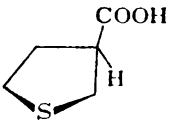
*R*-(−)-Tetral-1-ol (R = H; X = OH) (38)
*R*-(+)-2,2-Dimethyltetral-1-ol (R = CH ; X = OH) (37)
*R*-(−)-1-Aminotetralin (R = H; X = $NH_2$) (38)
*R*-(−)-1-Dimethylaminotetralin (R = H; X = $N(CH_3)_2$) (38)
*R*-(+)-Tetralin-1-carboxylic acid (R = H; X = COOH) (38)



*R*-(−)-2-Carboxyphenyl-1-tetralone (39)



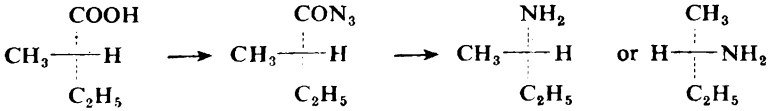
*R*-(−)-2-Methyl-2-ethylsuccinimide (24)



*S*-(+)-Thiophane-3-carboxylic acid (40)

A requisite condition for chemical correlations has long been considered to be the use of such reactions in which the bonds of the four substituents to the asymmetric centre are not broken. If this condition was not followed, there was no certainty that there would be no change of configuration (Walden inversion). The situation has now somewhat changed; reactions affecting the asymmetric centre may be used for configurational determinations provided that the mechanism and stereochemical result have been reliably established, i.e., if it is known whether they proceed with retention or inversion of configuration.

As an example, let us consider the elucidation of the configuration of 2-aminobutane on the basis of the known configuration of 2-methylbutyric acid. The starting (+)-2-methylbutyric acid was converted into a hydrazide, from which, by means of the Curtius rearrangement, there was obtained (+)-2-aminobutane. Though one of the bonds to the asymmetric centre is broken during the rearrangement, the Curtius rearrangement is however known at present to proceed with retention of configuration:



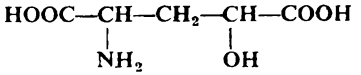
(+)-2-Methyl butyric acid

(+)-2-Aminobutane

An analogous procedure, i.e., a chemical change by way of a reaction in which the asymmetric centre is not left intact and no inversion of configuration is involved, was used for determining the configuration of γ-hydroxyglutamic acids XX.

The task here is somewhat more complicated since we are dealing not with two optical antipodes but with *four* substances characterized (in

aqueous solution) by the following values of optical rotation:

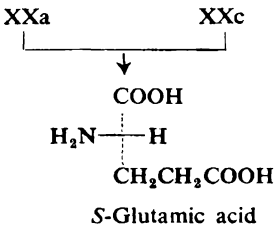


XX

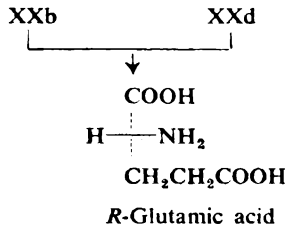
XXa = −22.3°
XXb = +21.5°
XXc = +31.8°
XXd = −31.2°

It is rather obvious that XXa and XXb, and XXc and XXd form, respectively, two pairs of optical antipodes (the small differences in the rotation values result from experimental errors).

The configuration of the asymmetric centre bearing an amino group is easily established by correlation with glutamic acid into which amino-hydroxy acids XX are converted after the elimination of the hydroxy group. In this process, the stereoisomers XXa and XXc give *S*-glutamic acid, while the stereoisomers XXb and XXd form *R*-glutamic acid:

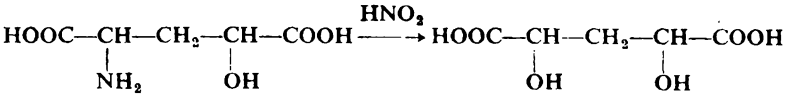


*S*-Glutamic acid



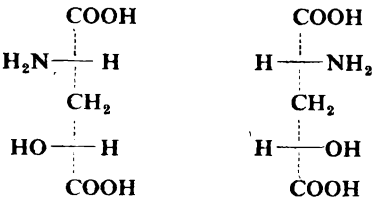
*R*-Glutamic acid

To determine the configuration of the second asymmetric centre which carries a hydroxy group, the amino group is replaced with a hydroxy group by the action of nitrous acid, which gives a dihydroxy acid:

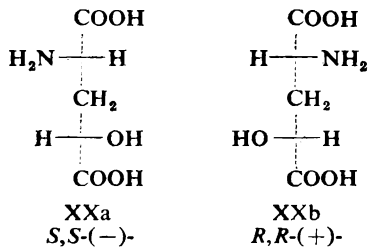


This reaction affects the asymmetric centre but is known to proceed with retention of configuration. The stereochemical result of the reaction is as follows: from acids XXc and XXd there is obtained the *meso*-form of the dihydroxy acid. Knowing (on the basis of correlation with glutamic acid) the configuration of the amine asymmetric centre, we

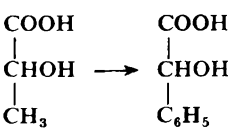
can thus write the configuration of the second asymmetric centre as well:




Recall that stereoisomer XXc is converted, after the hydroxy group is removed, into the same *S*-glutamic acid that is given by stereoisomer XXa; hence, XXa and XXc are diastereomeric and differ in the configuration of the hydroxyl asymmetric centre. This gives the configuration XXa, and the analogous reasoning as to the diastereomeric relations between XXb and XXd yields the configuration of XXb.

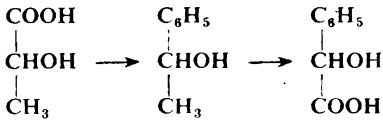



Not infrequently correlations of configurations require much ingenuity. Suppose, for example, that we are to convert lactic acid into mandelic acid without disturbing the asymmetric centre:

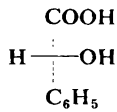



When looking at the scheme written above it may seem that this is impossible because for this to be done, one would think that the methyl group must be replaced by a phenyl group, in which case the asymmetric

centre would inevitably have to be affected during the course of this replacement. Nontheless, such a correlation has been accomplished: the carboxyl group was transformed into a phenyl group and the methyl group oxidized to the carboxyl group:

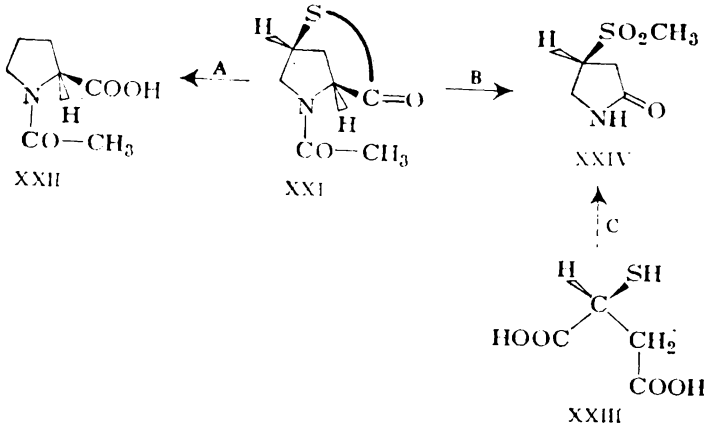


Of course, each of the conversions marked with an arrow in fact involved a number of multi-stage reactions, the stereochemical result of which was eventually found to be the following: from *S*-(+)-lactic acid there was obtained levorotatory mandelic acid, which unambiguously specifies its configuration:



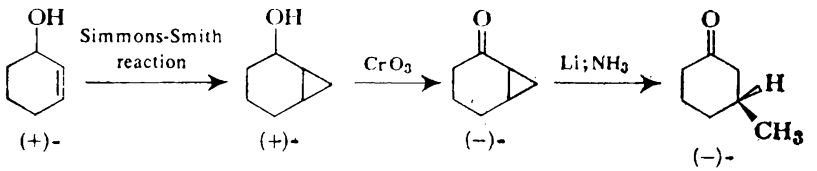
R-(−)-Mandelic acid

A great deal of ingenuity had to be displayed by Yamada *et al.* (41) in determining the configuration of mercaptosuccinic acid. The key compound used by these authors was compound XXI which was converted by one series of reactions (pathway *A*) into a compound of known configuration, L-(—)-proline XXII, and correlated, via another series of reactions (pathways *B* and *C*), with (—)-mercaptosuccinic acid XXIII:



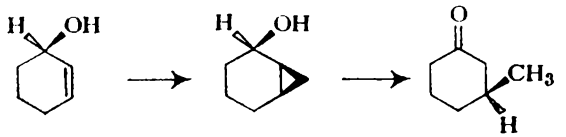
In this experiment the pathways *A*, *B*, and *C* (marked with arrows in the scheme) involve many stages which will not be considered here. The stereochemical result of this work may be stated as follows: the relation of compound XXI to (—)-proline enables the configuration of the sulphur-containing grouping to be determined. Since the configuration of (—)-proline is known and the bridge linking the sulphur atom to the CO group in (—)-XXI requires that the sulphur atom be on the same side of the ring as the COOH group of proline, then this relation enables determining the configuration of the sulphur-containing side chain. The pathway *B* involves the removal of one of the two asymmetric centres of XXI (the asymmetric centre of proline) and the formation of compound (—)-XXIV with one asymmetric centre needed for correlation with mercaptosuccinic acid. It is exactly this correlation that is effected by route *C*, (—)-mercaptosuccinic acid XXIII being correlated with (—)-XXIV. The procedure used may be called the method of replacement of the asymmetric centre. Indeed, the asymmetric centre of proline disappears in the course of the conversion, being replaced by another, sulphur-containing asymmetric centre which is in strict configurational relationship to the one displaced.

Another example of replacement of the asymmetric centre has been described by Hill and Morgan (42) who were concerned with the determination of the configuration of cyclohex-2-en-1-ol. The dextrorotatory isomer of this alcohol was converted into levorotatory 3-methylcyclohexanone, the configuration of which is known:



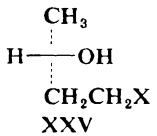

The use of this sequence of conversions for configuration determinations became possible owing to the knowledge of the steric direction of the first reaction: when such compounds are subjected to the Simmons-Smith reaction, the cyclopropane ring is invariably formed in the *cis*-position to the hydroxyl group present. Thus, instead of the position of the hydroxyl group relative to the ring (and this is what determines the configuration of cyclohex-2-en-1-ol), it is sufficient to know the position of the cyclopropane ring in the derivative formed. For this position to be established, the bicyclic alcohol is converted, by means of the subsequent two reactions (by removing the "old" asymmetric centre, the new asymmetric centre being left intact), into (—)-3-methylcyclohexanone, whose configuration is known. At the same time, from the stereo-

specificity of the Simmons-Smith reaction it follows that the OH group in the original compound must be on the same side of the cyclohexane ring as the $CH_3$ group in (—)-3-methylcyclohexanone:




### 3.3.2. METHOD OF OPTICAL COMPARISON

Apart from direct chemical transformations, the configurations of optical antipodes can also be determined by using indirect methods based on the analysis of certain regularities in the physical properties of compounds. First, use may be made of the regularities of optical rotation itself. Such regularities were established as early as the last century by L.A. Chugaev (Tschugaeff, 43). Chugaev found, in particular, that in a homologous series the magnitude of molecular rotation is nearly constant (the rule of constancy of molecular rotation); see also page 278. The second Chugaev rule, which is especially important for configuration determinations, is known as the Distance Rule. According to this rule, the effect of a given structural change on the contribution of an asymmetric centre to optical rotation decreases the further the centre of the change is from the asymmetric centre. Thus, optical rotation is primarily determined by the nearest environment of the asymmetric centre. For example, many compounds of the general formula XXV have a right-handed rotation, independently of the nature of substituent X (X = halogen atom, amino group, carboxyl group, carbamide group).




XXV

The Distance Rule discovered by Chugaev is not infrequently termed the vicinal effect (or vicinal action) and considered to have been formulated by Freudenberg. In actual fact, Freudenberg's merit lies not in the discovery but in the wide application of the rule in configurational studies. The *method of optical comparison* developed in the works of Freudenberg is based on the use of the following rules which directly follow from the general regularities discovered by Chugaev:

1. Like structural changes in like molecular surroundings cause similar shifts in molecular rotation. This is the so-called *Rule of Shift* (Displacement Rule).

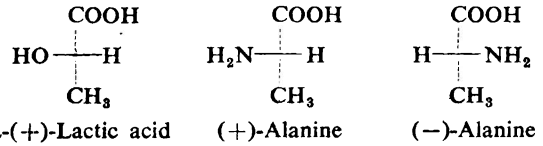
2. The optical rotation of structurally related compounds of identical configuration undergoes analogous changes under the influence of the solvent, temperature or other factors.

Using the method of optical comparison, Freudenberg established (44), in particular, the configurational relation between hydroxy and amino acids, which could not be done at that time by means of a direct chemical conversion since such a conversion affects the asymmetric centre, and the data on reaction mechanisms were not as reliable as they are now. Table 3.1 lists values of optical rotation for a number of derivatives of lactic acid (as a compound of known configuration) and two antipodes of alanine, whose configurations were to be determined in the work mentioned.

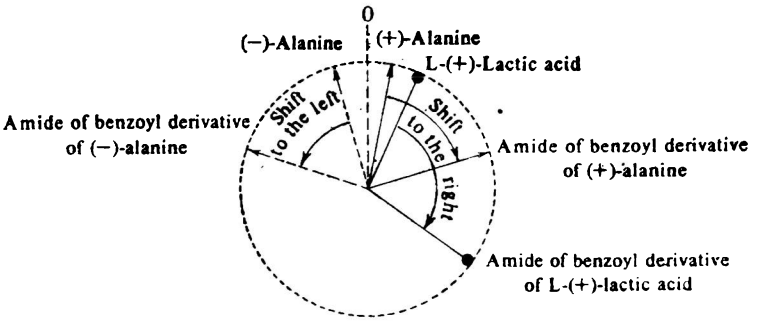
TABLE 3.1. MOLECULAR ROTATIONS OF DERIVATIVES OF L-(+)-LACTIC ACID AND ALANINE

| Substituent at OH or $NH_2$ group | Substituent at COOH group | $[M]_{Hg}$ of derivatives of | | |
|---|---|---|---|---|
| | | L-(+)-lactic acid | (+)-alanine | (−)-alanine |
| $C_6H_5CO$— | —$NH_2$ (amide) | +135° | +93° | −93° |
| $C_6H_5CO$— | —$C_2H_5$ | +59.5° | +107° | −107° |
| $C_6H_5CO$— | —$CH_3$ | +43.5° | +15° | −15° |
| $CH_3CO$— | —$C_2H_5$ | −80.9° | −84° | +84° |
| *p*-$CH_3C_6H_4SO_2$— | —$C_2H_5$ | −123° | −104° | +104° |

From the data given in Table 3.1 it is seen that the rotation gradually shifts to the left (when considering the derivatives of L-(+)-lactic acid in the order in which they are listed in the table) — from the more positive to the less positive and then to the negative values. The same shift is observed in the series of derivatives of (+)-alanine. Hence, the configurations of (+)-lactic acid and (+)-alanine are identical, which allows us to write the following configurational formulas for alanine:



It is important to understand that for a configurational relationship to be established, not the simple fact of coincidence of rotations in sign is essential, not their increase or decrease, but the *direction of shift* (to the right or left in an arbitrary series identical for the two compounds being compared). This may be illustrated by the following scheme:



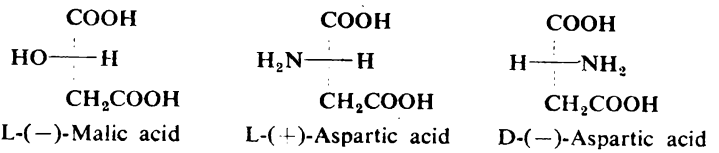

An analogous comparison has been made for the pair L-(—)-malic acid and aspartic acid (45). The diethyl esters of these acids were compared, which contained different substituents at the hydroxyl group (or, accordingly, at the amino group) (Table 3.2).

TABLE 3.2. MOLECULAR ROTATIONS OF DERIVATIVES OF L-(—)-MALIC AND ASPARTIC ACIDS

| Substituent at hydroxyl or amino group | $[M]_{578}$ of derivatives of | | |
|---|---|---|---|
| | L-(—)-malic acid | (+)-aspartic acid | (—)-aspartic acid |
| $C_6H_5CH{=}CHCO$— | −13° | +20° | −20° |
| $C_6H_5CO$— | −28° | +12° | −12° |
| HCO— | −58° | −13° | +13° |
| $CH_3CO$— | −68° | −18° | +18° |
| $n$-$C_8H_{17}CO$— | −70° | −20° | +20° |
| $C_2H_5SO_2$— | −101° | −31° | +31° |
| $p$-$CH_3C_6H_4SO_2$— | −101° | −36° | +36° |

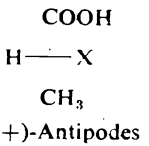
From the data presented in Table 3.2 one can easily see that the left-handed rotation gradually increases in the series of derivatives of L-(—)-malic acid, whereas in the series of derivatives of (+)-aspartic acid the same shift (to the left) reveals itself in a constant decrease of the right-

handed rotation and then in an increase of the left-handed rotation. Thus, of the enantiomeric aspartic acids the dextrorotatory one has the same configuration as L-(—)-malic acid:




Later, Freudenberg used the method of optical comparison in correlating the configurations of hydroxy and halogen-substituted acids (which cannot be done directly by chemical means either without disturbing the asymmetric centre).

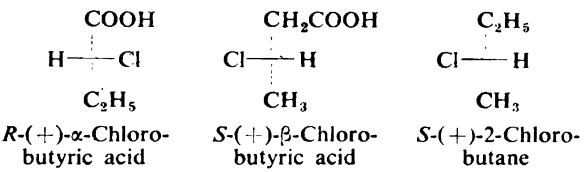
The following configuration has been proved for α-halogen-substituted acids:




R-(+)-Antipodes

where X = chlorine, bromine, iodine, or azido group.

The configurations of other compounds with a halogen atom attached to the asymmetric centre have also been determined by means of the optical comparison method:

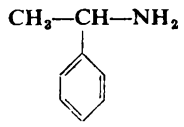



*R*-(+)-α-Chloro-butyric acid | *S*-(+)-β-Chloro-butyric acid | *S*-(+)-2-Chloro-butane

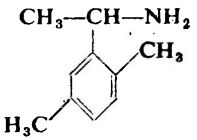
The optical comparison method is a quite reliable tool for configuration determinations. It must however be used with great caution and a thorough comparison is to be made on the maximum possible number of derivatives. When comparing compounds with different substituents attached to the asymmetric centre, one must be especially careful in selecting derivatives and the procedure used. Thus, a hydroxyl-containing compound liable to undergo association cannot be directly compared with a chlorine derivative: the hydroxyl group should first be converted into an ether or ester grouping. In order to preclude the specific effect of the solvent, liquid derivatives may be measured without the solvent, or use may be made of nonpolar inert solvents, say, hexane or isooctane.

On the other hand, the effect of the solvent on the magnitude of optical rotation may also be used, as suggested by Leithe (46), for configuration

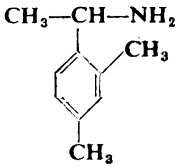
determinations. Let us consider this variant of the method of optical comparison for determination of the configuration of ring-substituted analogues of α-phenylethylamine:



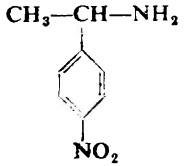
XXVI



XXVII



XXVIII



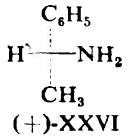
XXIX

The configuration of α-phenylethylamine XXVI was known (38). For the configurations of its analogues, XXVII-XXIX, to be determined, the changes of optical rotation caused by the solvent were compared for benzoyl derivatives of amines (Table 3.3).

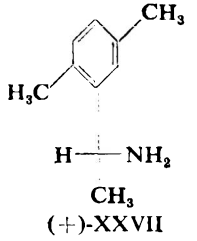
TABLE 3.3. SPECIFIC ROTATIONS OF BENZOYL DERIVATIVES OF α-PHENYLETHYLAMINE AND ITS ANALOGUES IN VARIOUS SOLVENTS

| Solvent | $[\alpha]_D$ of benzoyl derivatives of amines | | | |
|---|---|---|---|---|
| | XXVI | XXVII | XXVIII | XXIX |
| Benzene | +39.9° | +74.7° | +37.7° | +30.5° |
| Ethanol | −0.3° | −1.6° | −15.0° | −15.8° |
| Methanol | −8.4° | −2.3° | −17.9° | −19.4° |
| Acetone | −28.1° | −28.6° | −35.8° | −41.0° |

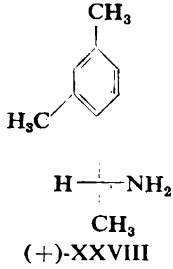
In all cases the rotation is positive in benzene; in alcohols and in acetone the sign of rotation is reversed. Thus, amines having one sign of rotation are of identical configuration, i.e. (47):



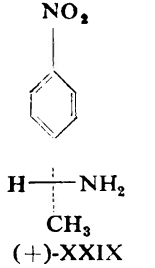
(+)-XXVI



(+)-XXVII



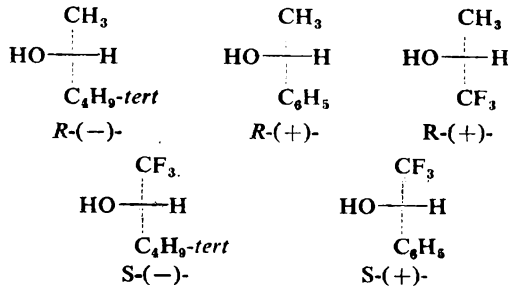
(+)-XXVIII



(+)-XXIX

The inference for *p*-nitroamine XXIX has also been confirmed by its direct preparation from optically active α-phenylethylamine.

The method of optical comparison has also been employed for the correlation of the configurations of the following alcohols and their trifluoromethyl analogues (48):




The use of different symbols (*R* and *S*) for compounds of identical configuration is associated with the change of the priority of substituents upon replacement of $CH_3$ by the $CF_3$ group (here the *R,S*-system is not so prominent).

On the basis of the general rule stating that compounds of identical configuration show the same changes in rotation under the influence of the same factors, there have been worked out a number of more concrete rules referring to individual groups of compounds. One of these rules refers to amino acids and states that the optical rotation of all natural amino acids (L-series) in acid solutions shifts to the right. Let us recall once again: this rule should not be understood in the sense that there is necessarily an increase in the right-handed rotation: the shift to the right may also imply a decrease in the left-handed rotation. Data on the rotation of some L-amino acids in neutral and acid solutions are given in Table 3.4.

The **Amide Rule** as formulated by Freudenberg states: the optical rotation of the amides of α-hydroxy acids of the D-series is always shifted to the right as compared with the rotation of the corresponding hydroxy acids. The rule may be illustrated by the data presented in Table 3.5.

These data can be used to confirm the configuration, say, of mandelic acid. Of its two antipodes the levorotatory form shows a shift of rotation to the right upon conversion into an amide. Hence, (—)-mandelic acid has the D-configuration. The same applies to (—)-hexahydromandelic acid:

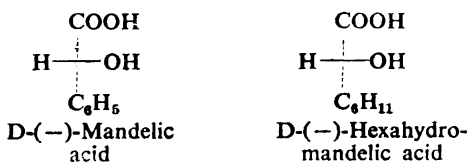


TABLE 3.4

| Amino acid | $[\alpha]_D^{20}$ in water | $[\alpha]_D^{20}$ in HCl |
|---|---|---|
| Alanine | +2.7° | +14.3° |
| Serine | −6.8° | +14.4° |
| β-Chloro-α-aminobutyric acid | −15.5° | +0.8° |
| α-Aminobutyric acid | +8.0° | +19.6° |
| Valine | +6.4° | +28.7° |
| Leucine | −10.3° | +15.6° |
| Isoleucine | +11.3° | +40.6° |
| Asparagine | −4.9° | +28.5° |
| Aspartic acid | +4.3° | +25.7° |
| Glutamic acid | +9.9° | +30.8° |
| Phenylalanine | −35.3° | −7.1° |
| Phenylglycine | +112.6° | +158° |

Had we used the older Hudson formulation of the rule ("the amides of all α-hydroxy acids of the D-series have a right rotation"), we would have arrived at a wrong conclusion about the configuration of mandelic and hexahydromandelic acids.

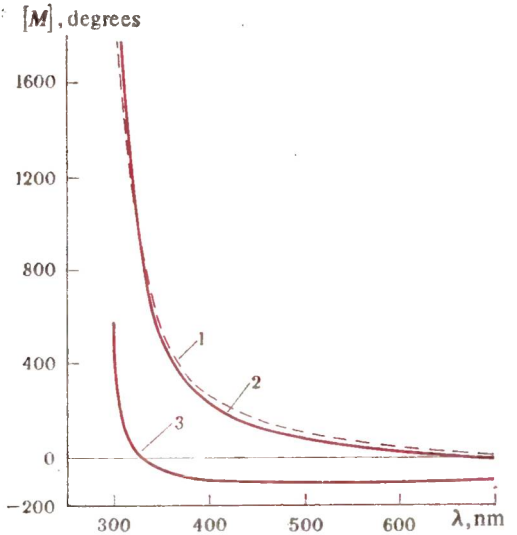
The Ester Rule states that in the esterification of hydroxy acids of the D-series with methanol there is observed a shift of rotation to the right; when the esterification is carried out with ethanol, the shift to the right increases.

TABLE 3.5

| Hydroxy acid | $[\alpha]_D$ of acid | $[\alpha]_D$ of methyl ester |
|---|---|---|
| D-Lactic acid | −4° | +22° |
| D-Glyceric acid | −2.1° | +66° |
| D-Malic acid | from +3° to −3°* | +40° |
| D-Tartaric acid | from +6° to +14°* | +64° |
| Monoamide of D-tartaric acid | +64° | +106° |
| (−)-Mandelic acid | −153° | −95.5° |
| (+)-Mandelic acid | +153° | +95.5° |
| (−)-Hexahydromandelic acid | −26.6° | +41.7° |

* Depending on concentration and temperature.

Figure 3.1.




*The optical rotatory dispersion curves of α-(iodophenoxy)-propionic acids:* 1 — meta-*isomer*; 2 — para-*isomer*; 3 — ortho-*isomer*.

### 3.3.3. DETERMINATION OF CONFIGURATIONS BY THE SPECTROPOLARIMETRIC METHOD

The changeover from a comparison of rotations at a single wavelength to a comparison of optical rotatory dispersion curves (ORD curves) increases the reliability of configuration determination by comparison of optical rotation. A good example is afforded by iodophenoxypropionic acids studied by Sjöberg (49) at the very beginning of the development of spectropolarimetry. The ORD curves of the three structurally isomeric acids differing in the position of iodine in the benzene ring are given in Fig. 3.1.

The curves shown in Fig. 3.1 have an identical course for all the three structural isomers and so we may conclude that the *ortho*-isomer which rotates to the left at the sodium D line has the same configuration as the dextrorotatory *meta*- and *para*-isomers. Evidently, had we relied only on the signs of rotation at the sodium D line and used the erroneous reasoning that "closely related" compounds of the same configuration must have the same sign of rotation, the conclusion about the configuration of the *ortho*-isomer which "does not obey the rule" would have been wrong.

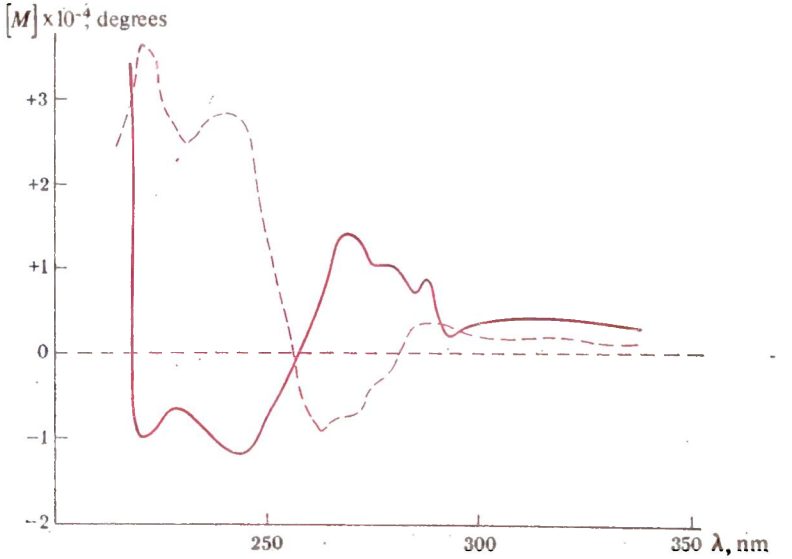
Interesting configurational features have been revealed with the aid of spectropolarimetry for derivatives of partially hydrogenated carbazole. The starting point was compound XXX, in which the configuration

of the asymmetric centre at $C_{4a}$ was known (50). The compound XXX when heated with formic acid gives a formyl derivative XXXI (with the isomerization of the double bond):

XXX XXXI

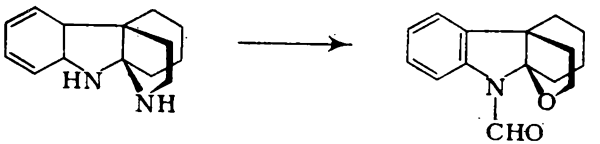
If compound XXXI is allowed to react with water or methanol, the addition of the elements of water or alcohol to the double bond will result in the formation of a new asymmetric centre at atom 9a. The resulting compounds, XXXII and XXXIII, have the same sign of rotation in the long-wavelength region of the spectrum: it would be logical to assume that the two closely related compounds must have the same configuration. A study of the ORD curves has shown, however, that the curves are "enantiomeric" and that therefore the two compounds have opposite configurations at atom 9a (Fig. 3.2.) (51).

Figure 3.2.



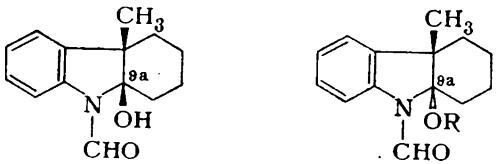

*The optical rotatory dispersion curves of hydrogenated carbazoles XXXII (the solid curve) and XXXIII (the dashed curve).*

The configurations of the compounds in question have been conclusively established by comparing the ORD curves of compounds XXXII and XXXIII with the curve of compound XXXIV obtained from the alkaloid (+)-echiboline XXXV, a compound of known configuration.




(+)-XXXV XXXIV

The compound XXXIV has an ORD curve identical with the ORD curve of compound XXXII and, hence, they have the same configuration at atom 9a. Accordingly, compound XXXIII must have a configuration at atom 9a opposite to that of XXXII (52).




XXXII XXXIII

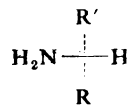
Rotatory-dispersion measurements have been used to elucidate the configuration of a number of alcohols containing aryl radicals. The ORD curves of alcohols of known configuration

*R*-(+)-α-Phenylethanol *R*-(+)-Phenylcyclohexylcarbinol

were compared with the ORD curves of related alcohols, which enabled the following configurations to be assigned to the alcohols under study (53):

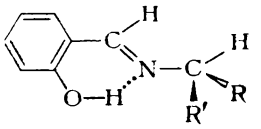
*R*-(+)-Phenylisopropylcarbinol *R*-(+)-*o*-Tolylcyclohexylcarbinol

A study of the ORD curves of Schiff's bases in the region of 600-300 nm has made it possible to formulate an empirical rule (54), according to which the salicylidene derivatives of amines, which have the configuration



R and R′ are hydrocarbon radicals, R being larger than R′

are characterized by negative ORD curves. Later, this conclusion was supported in a series of works by Smith and his coworkers, who succeeded in carrying out measurements in the shorter-wavelength region by finding the corresponding Cotton effects. According to these authors (55), the most stable conformation of the salicylidene derivatives of amines is the one in which the hydrogen attached to the asymmetric centre lies in the same plane as the aromatic ring and the chelate ring:



$R = C_2H_5, C(CH_3)_3, CH_2OH, C_6H_5$

$R' = CH_3, C_2H_5$

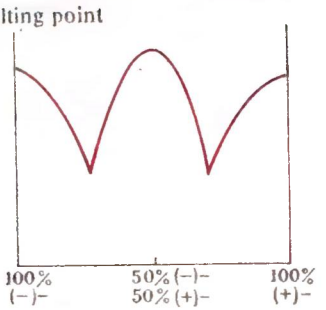
If the larger radical (R) is behind the plane of the drawing, then the Schiff's base has *positive* Cotton effects at 315 and 255 nm.

### 3.3.4. THE METHOD OF QUASI-RACEMATES

When the optical antipodes of a substance are mixed, systems of three types may be formed: a conglomerate, a racemic compound, and a racemic solid solution (a pseudo-racemic compound). Each of the three types of systems has a characteristic melting-point diagram (see page 50). It will be recalled that a racemic compound is a molecular compound of two antipodes. Being a chemical substance, a racemate has certain physical constants which differ from the corresponding constants of the antipodes. It is characterized, in particular, by a certain melting point (Fig. 3.3), which may be either higher or lower than the melting points of the antipodes.

**Quasi-racemic compounds** (or *pseudo-racemates*) are molecular compounds which differ not too strongly from true racemates (racemic compounds) only in the structure of one of the components. In other words, a quasi-racemate is a true-racemate-like molecular compound formed between the optical antipodes of different (but related) compounds. A quasi-racemate has a melting-point curve resembling the curve of a true racemate.

Figure 3.3.

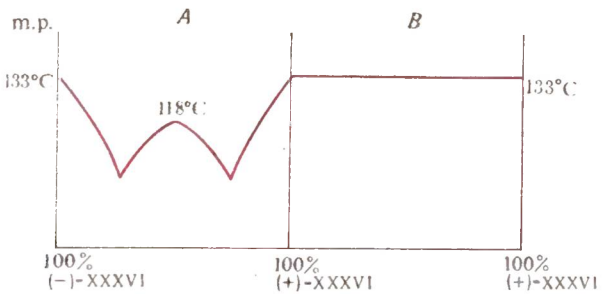



*Melting-point diagram of a racemate.*

The principle of using quasi-racemates for configuration determinations consists in the following. If the antipodes of two chemically related compounds are mixed, this may give rise to a molecular compound — a quasi-racemate, the melting-point diagram of which will be reminiscent of the melting-point diagram of a true racemic compound. Thus, revealing the character of the melting diagram, it is possible to find out whether the substances mixed were antipodes or not and to establish the configuration of one of the substances if that of the other is known.

For example, the mixing of the antipodes of mandelic acid XXXVI yields a racemic compound with a characteristic melting-point curve (Fig. 3.4*A*). The right-hand part (B) is a "melting-point diagram" in which the same antipode of mandelic acid is shown on the left and right of the horizontal axis. Actually, there is of course no mixing here:

Figure 3.4.



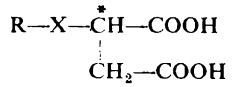

*Melting-point diagrams of racemic DL-mandelic acid XXXVI (A) and pure (+)-mandelic acid (or (−)-antipode) (B).*

the melting point of a pure antipode of mandelic acid is extended into a horizontal straight line. This procedure is used for a vivid comparison with what follows. If we prepare mixtures of (+)-mandelic acid, (+)-XXXVI, and (—)-hexahydromandelic acid, (—)-XXXVII, we shall obtain a melting-point curve resembling the curve of a true racemic compound (Fig. 3.5*A*). But if (+)-hexahydromandelic acid, (+)-XXXVII, is added to (+)-mandelic acid, (+)-XXXVI, the melting-point diagram will be similar to that shown in Fig. 3.4*B*, with the straight line being inclined (Fig. 3.5*B*). Since, according to the general rule, the configurations of compounds making up a quasi-racemate must be opposite, the following conclusion may be made: in our example (+)-mandelic and (—)-hexahydromandelic acids have opposite configurations. In other words, in this particular case the acids with the same sign of rotation have the same configuration.

For a quasi-racemate to be formed, the substances to be mixed must be chemically related, but this condition alone is not sufficient. The Swedish scientist Fredga, whose school developed the method of quasi-racemates (for a review, see ref. 56), believes that substances capable of forming true racemates (this ability is first of all displayed by polar molecules) are also generally liable to form quasi-racemates. Quasi-racemates can be formed by mixtures of substances whose crystals are isomorphous. These include members of a homologous series and also pairs of compounds which differ only in that the hydrogen is replaced by a chlorine, bromine, or iodine atom (but the molecule must not be too small).

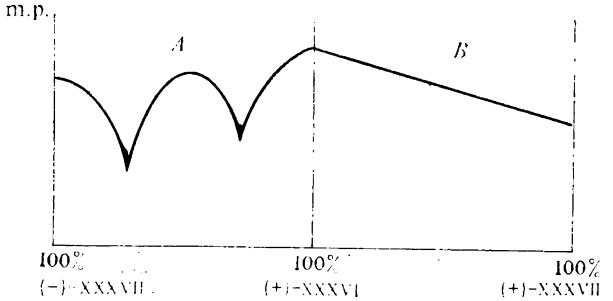
Like true racemates (racemic compounds), quasi-racemates may have different stability, which is reflected in melting-point diagrams. Typical curves for stable and unstable true racemates formed by the (+)- and (—)-forms of ethylxanthoalkanoic acids ($C_3$ and $C_4$) are shown in Fig. 3.6. Similar curves can be found among the melting-point diagrams of quasi-racemates.

The quasi-racemate method is most interesting in that it may be applied to compounds that cannot be correlated by a direct chemical transformation. This refers, for example, to compounds of the following type:



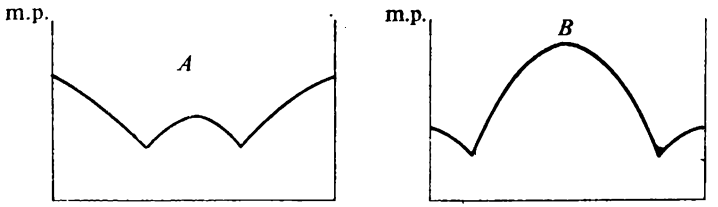
where X is an oxygen or sulphur atom or NH group. A comparison of the melting-point diagrams of mixtures of these compounds makes it possible to correlate the configurations of amino acids, hydroxy acids, and mercapto acids.

Figure 3.5.




*Melting-point diagrams of a mixture of (±)-mandelic acid, (+)-XXXVI, and (−)-hexahydromandelic acid, (−)-XXXVII (A), and of a mixture of (+)-mandelic acid, (±)-XXXVI, and (±)-hexahydromandelic acid, (+)-XXXVII (B).*

Figure 3.6.




*Melting-point diagrams of a mixture of (+)- and (−)-forms of ethylxanthopropionic acid (A, unstable racemate) and of a mixture of (±)- and (−)-forms of ethylxanthobutyric acid (B, stable racemate).*

Figure 3.7 shows the melting-point diagrams of ethylxanthate derivatives (R = $C_2H_5S$—CS—) of malic acid XXXVIII and aspartic acid XXXIX. From these diagrams it follows that a quasi-racemate is formed by mixing derivatives of acids with the same sign of rotation. Hence, having the same sign of rotation, malic and aspartic acids have opposite configurations. Assuming that the configuration of malic acid is known from its correlation with tartaric acid, we can write the configuration of aspartic acid:

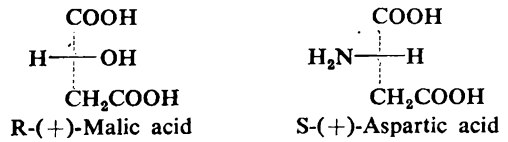
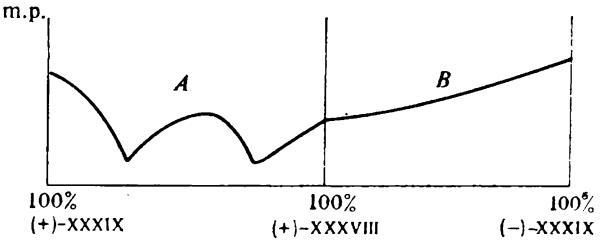
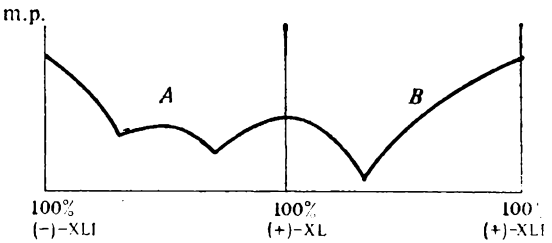


Figure 3.7.




*Melting-point diagrams of ethylxanthic derivatives of malic acid (XXXVIII) and aspartic acid (XXXIX).*

Figure 3.8.



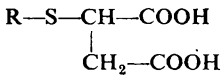

*Melting-point diagrams of ethylxanthic derivatives of malic (XL) and mercaptosuccinic (XLI) acids.*

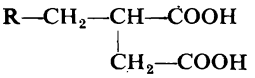
These data and also an analogous study of the derivatives of lactic acid and alanine have confirmed the configurational relationships between hydroxy and amino acids, obtained earlier by Freudenberg who used the method of optical comparison.

The melting-point curves of mixtures of ethylxanthate derivatives of malic (XL) and thiolsuccinic (XLI) acids are less pronounced (Fig. 3.8). Nonetheless it can be established that a quasi-racemate is formed by mixing derivatives of acids having opposite signs of rotation. Hence, based on the known configuration of malic acid, we may write the configuration of thiolsuccinic acid:

*R*-(+)-Mercaptosuccinic acid
(*R*-(+)-thiolsuccinic acid)

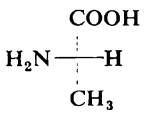
The derivatives of thiolsuccinic acid occupy a special place in configurational studies carried out by means of the method of quasi-racemates. Having established the configuration of compounds of this type, Matelle compared S-alkylthiosuccinic acids with alkylsuccinic acids relating for the first time the configuration of compounds with a tertiary asymmetric centre to the configuration of compounds containing a secondary asymmetric atom:

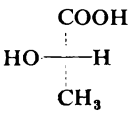


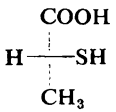



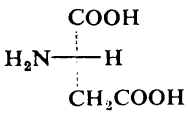

The thus deduced configuration of alkylsuccinic acids coincides with the configuration found by Freudenberg (see pages 192-193).

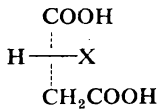
Omitting the details of numerous configuration determinations carried out by the method of quasi-racemates, we shall mention only the most important results. All the projection formulas given below represent dextrorotatory antipodes:



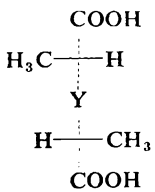



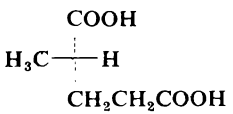



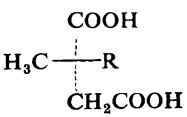




(X = OH, SH, Cl, Br, alkyl groups, $C_1$-$C_6$)

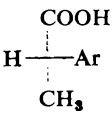



(Y = O, S, $CH_2$)



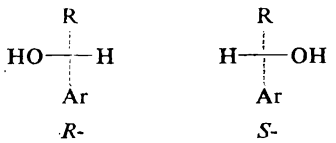




(R = $C_2H_5$, *iso*-$C_3H_7$)



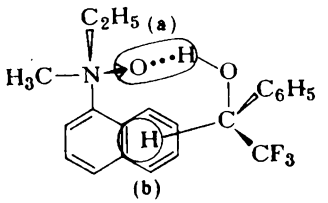

(Ar = phenyl, 2-naphthyl, 3-indolyl, etc.)

As known (see page 59), enantiotopic protons can be detected by measuring NMR spectra in chiral solvents. The relative position of signals depends on the configuration of compounds. For example, if the alcohols




are dissolved in optically active *R*-(+)-α-(1-naphthyl)-ethylamine, the signal of the methine proton of the alcohol of *R*-configuration is found to be in a stronger field than the corresponding signal of the *S*-enantiomer (57).

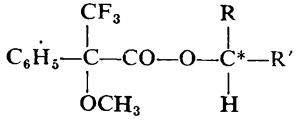
Another optically active solvent widely used for NMR is S-(+)-2,2,2-trifluoro-1-phenylethanol. This solvent was used, for example, for determining the configuration of N-oxide of α-(N-methyl-N-ethylamino)-naphthalene. The interaction between the solvent and the solute leads to the formation of a solvate, the conformation of which is fixed by the interaction at two points — between the hydroxyl group and the oxygen atom of the N-oxide (*a*) and between the acidic methine hydrogen and the π-electron system of the naphthalene ring (*b*):

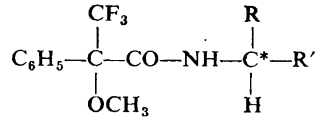



With the *S*-configuration of the oxide, shown in the scheme, its $C_2H_5$ group is in the *cis*-position to the phenyl ring of the solvent (both groups are behind the plane of the drawing). This neighbourhood leads to a shift of the signals of the $C_2H_5$ group by about 0.02 ppm to the side of strong fields as compared with the solvate of the oxide of opposite configuration (58).

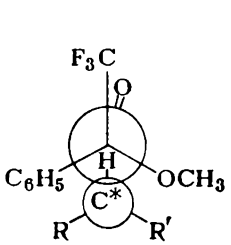
Another version of the use of NMR spectra for configuration determination is based on the formation of diastereomers and the comparison of the chemical shifts of diastereotopic groups. Thus, for example, for the configurations of alcohols or amines to be determined, they are con-

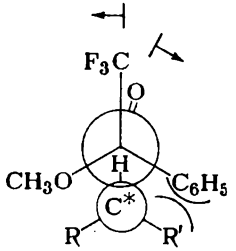
verted into esters or amides, respectively, by the reaction with *R*- and *S*-α-methoxy-α-trifluoromethyl-α-phenylacetic acid (59):





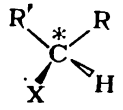
These esters (amides) exist in the following conformations:



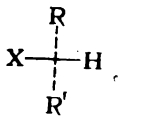


R′ > R

In the derivative of the *S*-acid (the formula on the right), because of a greater repulsion between R′ and $C_6H_5$, the $CF_3$ group is found to be more remote from the carbonyl group than in the derivative of *R*-configuration. As a result, the $CF_3$ group in the derivative of *S*-configuration is in a less deshielding environment and the signal of $^{19}F$ is in a stronger field than in the diastereomer having the *R*-configuration of the acid. If the ratios of the NMR signals indicated are observed, then the configuration of the alcohol (amine) corresponds to that adopted in the above schemes, i.e.,



or



where X = OH or $NH_2$

With the opposite configuration of the alcohol (amine) the relations between the positions of the signals of diastereomeric esters (amides) will naturally be opposite.

### 3.3.6. STEREOSPECIFIC ASYMMETRIC SYNTHESIS

In this method, use is made of the well-known fact that the rates of formation of diastereomers are, as a rule, different (see page 52). Červinka (60), while acylating alcohols or amines with *S*-(+)-hydratropic acid in

the presence of cyclohexylcarbodiimide, found that alcohols and amines of *R*-configuration enter into reaction more rapidly. Compounds of *S*-configuration accumulate in the unacylated product; one has only to determine the sign of rotation of the residue in order to relate it to the configuration. Alcohols and amines of *S*-configuration have been shown by this method to exhibit a rotation to the left:

R — X = OH or $NHCH_3$;
H — X — R = $CH_3$, $C_2H_5$, cyclohexyl;
Ar — Ar = $C_6H_5$, *o*-, *m*-, *p*-tolyl,
*S*-(−)- — α-naphthyl

The use of other reactions of asymmetric synthesis has also been suggested for the elucidation of the configurations of compounds (61). The results available are however contradictory and care should be exercised when dealing with data obtained by this method (62).

There are many reviews devoted to this subject; the reader is referred, for example, to the article by W. Schlenk (63).

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CHAPTER 4

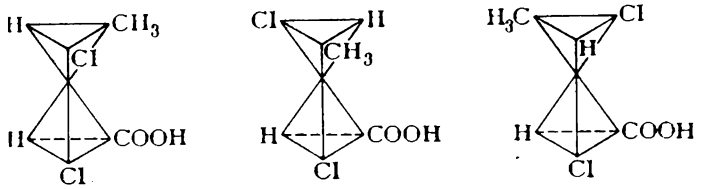
# Stereochemistry of Alkanes and Their Derivatives

The stereochemical specificity of compounds containing carbon chains manifests itself primarily in the existence of conformers, the nature of which has a substantial effect on the physical and chemical properties of compounds. A large number of acyclic compounds with one or more chiral centres are also known, which makes possible the existence of optical isomers and diastereomers. It is the specific stereochemical features of acyclic compounds that we are going to consider in this chapter.

In the early thirties of our century there appeared data contradicting the van't Hoff second postulate—the assumption of free rotation about single bonds. It is only the rejection of the van't Hoff second postulate that enabled Pitzer (1) to bring the experimentally found values of enthalpy and entropy of ethane into agreement with the calculated values. At a later time, the data on the existence of preferred conformations were obtained by spectral methods, dipole moment measurements and by other methods. The conformational theory is one of the most important theories in modern stereochemistry.

The first ideas of this kind, however, appeared in the last century. This is spectacularly demonstrated by the work of the German chemist Wislicenus published in 1888, in which he reasoned about the three mutual tetrahedral arrangements in the

product of addition of chlorine to crotonic acid and illustrated this with drawings which might be called today the representations of eclipsed conformations:




The model of cyclohexane in the form of a boat and chair suggested by Mohr in the last century also belongs to the field of conformational ideas (for details, see Chapter 5).

## 4.1. CONFORMATIONS OF ALKANES

From the physical standpoint, the energy of a molecule, $E$, in the various conformations is, in a general case, the sum of four contributions (2):

$$E = U_{nn} + U_{ee} + T - U_{ne}$$

where $U_{ne}$ = attraction of nuclei to electrons;
$U_{nn}$ = repulsion of nuclei from one another;
$U_{ee}$ = repulsion of electrons from one another;
$T$ = kinetic energy of electrons.

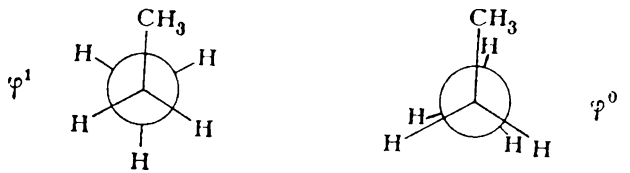
The observed energy of molecules is in a general case a minor difference between the much greater quantities—the energy of repulsion ($U_{nn} + U_{ee} + T$) and the energy of attraction $U_{ne}$. Thus, for ethane the maximum values of these energies are, respectively, equal to 95 kJ/mole and 82.4 kJ/mole; the difference between them (about 13 kJ/mole) is exactly the energy barrier that impedes free rotation in ethane. Such an analytical approach to the energy allows us to understand its extremely high sensitivity both to the structure of the molecule itself and to its environment (the state of aggregation, temperature, the nature of the solvent).

The instability of eclipsed conformations is usually believed to result from "steric hindrances"—the overlap of the van der Waals radii of eclipsed atoms or groups. This is what actually happens in many cases. The hydrogen atoms, however, are too small to create such steric hindrances in the eclipsed conformation of ethane. It has been calculated that the energy barrier thus formed must have been not more than 1.3 kJ/mole; but the actual magnitude of the energy barrier to rotation in ethane is 10 times greater—about 13 kJ/mole.

The problem of the physical nature of the energy barrier to rotation was for a long time the subject of discussion in the literature (for a review of works published in the fourties and fifties, see ref. 3). One of the explanations suggested was based on the conception of the repulsion between polarized C—H bonds; calculations however showed that for the required barrier height to be ensured the C—H bonds should have been practically completely of the ionic character, which of course contradicts reality. According to the present-day conceptions, the energy barrier in ethane is created by the quantum-mechanical forces of repulsion arising largely between the ς-electrons of the C—H bonds upon their approach in the eclipsed conformation (4).

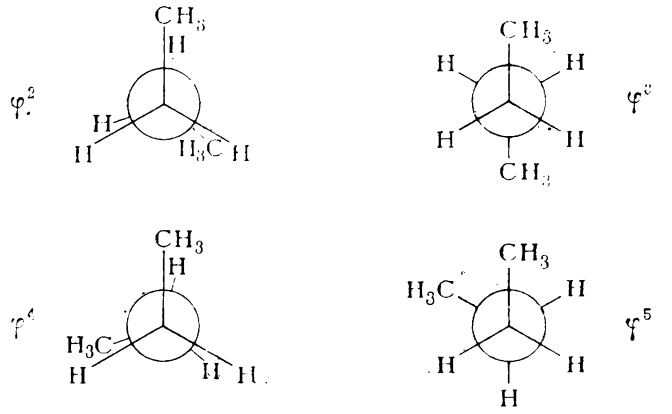
As has already been pointed out, the energy of the eclipsed conformation of ethane is 13 kJ/mole higher than the energy of the staggered (transoid or anti) conformation. It means that there is about 4 kJ/mole for each non-bonded H-H interaction in the eclipsed conformation.

Like ethane, propane may also have two conformations at the $C_1$—$C_2$ bond:




In the eclipsed $\varphi^0$-conformation, the energy of the propane molecule is 14 kJ/mole higher than in the $\varphi^1$-conformation. This additional energy is made up of two non-bonded H-H interactions (4 kJ/mole for each) and one H-$CH_3$ interaction. Hence, there is 6 kJ/mole for the latter interaction.

The *n*-butane molecule has three staggered and three eclipsed conformations (around the $C_2$—$C_3$ bond):

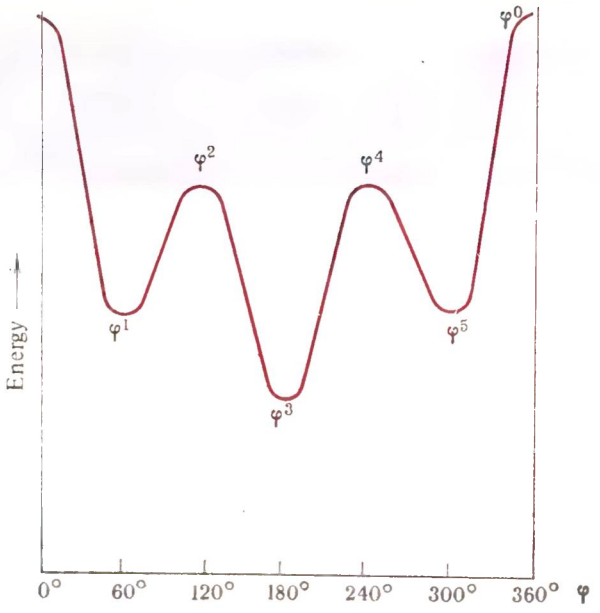


The energies of these conformations are given in Fig. 4.1. In the $\varphi^0$-conformation of *n*-butane, where the interaction of two methyl groups is involved, the potential barrier is even higher than in propane; according to different sources, it ranges from 18 to 26 kJ/mole. The energy of the skew $\varphi^1$- and $\varphi^5$-conformations is somewhat greater due to the skew interaction of the methyl groups; it is about 3.5 kJ/mole higher than in the staggered or anti ($\varphi^3$) conformation, which corresponds to an energy valley (an energy minimum) lower than the others. It is this energy (3.5 kJ/mole) which is called the **conformational energy** of butane: the energy difference between the conformers (the skew and the anti) is thus considerably lower than the barrier height that separates the conformations. The same relationships will be observed in all the other examples under consideration.

The conformational equilibrium, which will be discussed throughout this chapter, is the equilibrium between the anti or *transoid* ($\varphi^3$) and skew ($\varphi^1$) forms (there are, in fact, two skew forms but in the simplest cases they are mirror-image forms and do not differ in energy and therefore for simple compounds it will suffice to consider the two conformations indicated).

The position of the equilibrium between the skew and the anti conformation is determined by the difference in free energy between the two conformers — **the conformational free energy.** In calculating this energy it is necessary to take into account the fact that the entropy of the skew form (twice) is by $R \ln 2$ higher than that of the transoid form. The free energy difference between the skew and transoid conformations of *n*-butane is, according to new data (5), equal to $2.85 \pm 0.15$ kJ/mole and $\Delta S$ is 1.376 entropy units.

Figure 4.1.




*Energies of the various conformations of n-butane.*

Using the well-known relation between the free-energy difference and the equilibrium constant

$$K = e^{-\frac{\Delta F_0}{RT}}$$

it can be estimated that at room temperature the equilibrium constant in our example is equal to 3, i.e., for 3 molecules in the transoid conformation there is one molecule in the skew conformation.

To facilitate the conversion of the conformational energies to the ratios of conformers, Table 4.1 gives the corresponding numerical data.

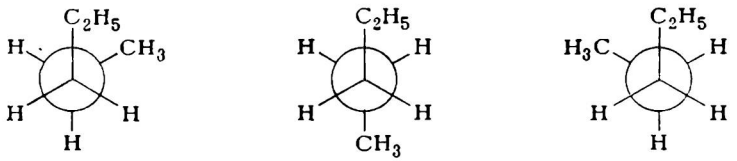
Having considered the conformations of the simplest hydrocarbons of the paraffin series—ethane, *n*-butane, and propane, let us now go further up the homologous series. The next member of the series, pentane, shows a new feature: here there are *two* "internal" C—C bonds, the free rotation about each of which may give rise to three conformations—$\varphi^1$, $\varphi^3$, $\varphi^5$. Hence, the following combinations are possible:

TABLE 4.1. THE RATIOS OF FREE-ENERGY DIFFERENCES AND THE EQUILIBRIUM OF CONFORMERS AT ROOM TEMPERATURE

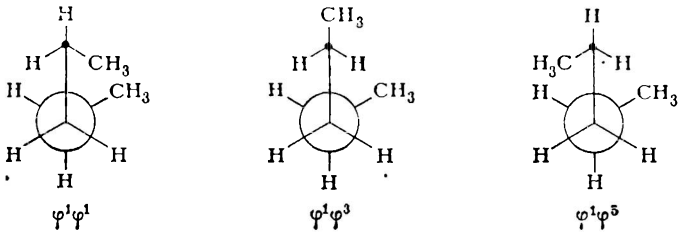
| $\Delta G_0^{298\ K}$ | | $K$ | Percentage content of stable form | $\Delta G_0^{298\ K}$ | | $K$ | Percentage content of stable form |
|---|---|---|---|---|---|---|---|
| kJ/mole | kcal/mole | | | kJ/mole | kcal/mole | | |
| 0 | 0 | 1.0 | 50 | 5.5 | 1.30 | 9.0 | 90 |
| 1.0 | 0.24 | 1.5 | 60 | 7.4 | 1.75 | 19.0 | 95 |
| 2.1 | 0.50 | 2.3 | 70 | 11.4 | 2.72 | 99.0 | 99 |
| 3.4 | 0.82 | 4.0 | 80 | 17 | 4.09 | 999.0 | 99.9 |

$\varphi^1\varphi^1$, $\varphi^1\varphi^3$, $\varphi^1\varphi^5$, $\varphi^3\varphi^3$, $\varphi^3\varphi^5$, and $\varphi^5\varphi^5$ (combinations with the superscripts transposed do not represent new conformations). How can this be pictured in the formulas?

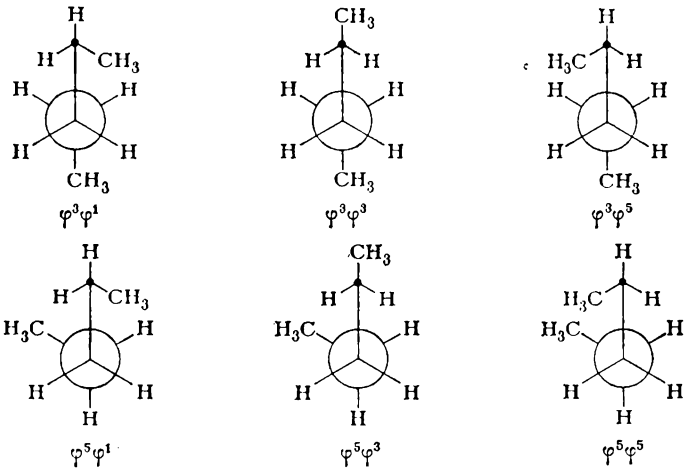
The Newman formulas are, in principle, designed for representation of conformers about one bond. In the case of *n*-pentane, the substituents in such a formula will be the $CH_3$ and $C_2H_5$ groups, which gives three conformations:




But the $C_2H_5$ group in its turn consists of $CH_2$ and $CH_3$ and may also exist in three conformations. The spatial structure of *n*-pentane with account taken of the conformations around both internal C—C bonds is conventionally represented as follows:

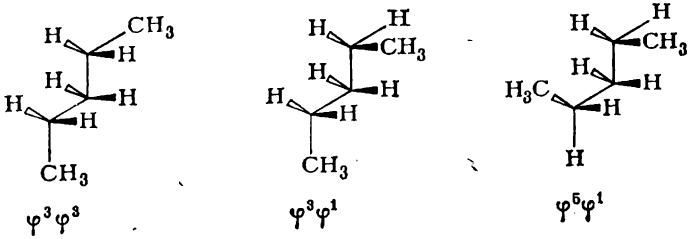



$\varphi^1\varphi^1$ $\varphi^1\varphi^3$ $\varphi^1\varphi^5$




Valuable information on the conformations of paraffins is furnished by infrared and Raman spectra. How these spectra change, depending on the specific conformational features of a substance will be seen at a later time on more suitable examples. At this point it will suffice to note that when a substance is frozen, i.e., upon transition from the liquid to the solid state, the infrared spectra of hydrocarbons are usually strongly simplified, the number of lines in them being decreased. This is evidence that in a crystal there ordinarily exists only one conformation, giving rise to its lines in the Raman and IR spectra. Thus, the study of both types of spectra of *n*-hexane has shown that the spectra are strongly simplified on freezing.

Using Raman and IR spectral data, the Japanese authors (6) have established that in the solid state, at —170°C, *n*-pentane exists in the ditransoid (anti-anti) conformation ($\varphi^3\varphi^3$); at room temperature there appear, in addition, two other conformers — the anti-skew ($\varphi^3\varphi^1$) and the (twice) skew ($\varphi^5\varphi^1$) conformations. The Newman formulas may be replaced by perspective formulas for representation of these conformations:

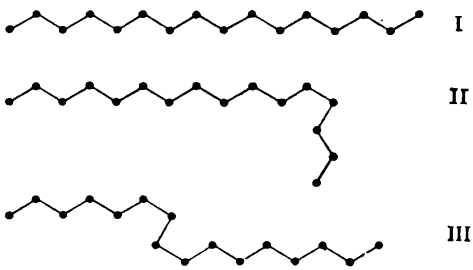


Attempts to represent the full conformation of a molecule such as hexane by means of Newman or perspective formulas lead to drawings of little value. The simpler way is usually chosen: use is made of a conventional planar scheme, for example:

Here *n*-hexane is pictured in the all-anti conformation, all its carbon atoms being arranged in the plane of the paper. In this conformation, the carbon chain forms a regular zig-zag line.

There is evidence of the conformations of paraffins containing an even larger number of carbon atoms. Up to a certain limit, they display the same specific features as does *n*-hexane, i.e., in the crystalline state they exist preferably in the zig-zag, all-anti conformation. On melting there appear other conformations, but if the number of carbon atoms is still relatively small, the zig-zag conformation prevails in the liquid state too.

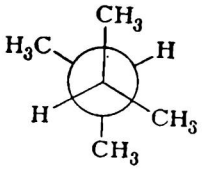
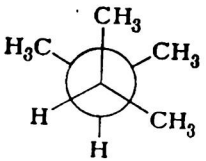
As the length of the carbon chain grows the existence of a regular, all-anti conformation becomes statistically less probable. Thus, in cetane, $C_{16}H_{34}$, in the liquid state, no zig-zag anti form I is present and there are only various irregular forms, say, II and III:



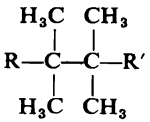

Though conformation I is, in principle, the most favourable, the mole cule does not assume this conformation because of the probability considerations. Conformations II and III are purely conventional representations of molecules in which the anti zig-zag is broken at one point; of course, there may be several such break points in the molecule. It should also be borne in mind that an irregular chain will not lie in a single plane, as is shown conventionally in our schemes.

Hydrocarbons with branched chains reveal conformational features of their own. As an example, we shall consider 2,3-dimethylbutane, the skeleton of which contains two branches. It has been found that the Raman and IR spectra of this compound do not change significantly with decreasing temperature and freezing. Hence, the conformational equilibrium is practically independent of temperature and this may be

observed if the energies of the conformers are very close. The following are evidently such conformers:

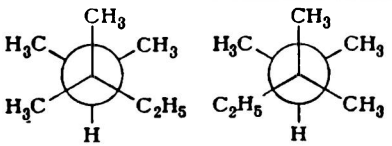
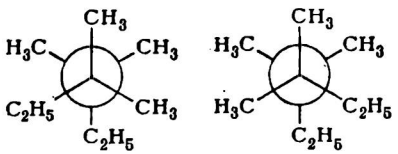
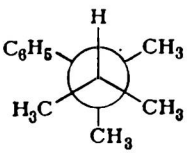
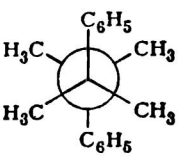



Data on the conformations of strongly branched hydrocarbons of the type

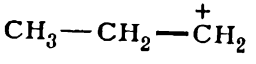


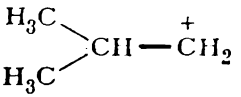
are presented in Table 4.2 (7).

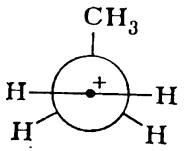
TABLE 4.2

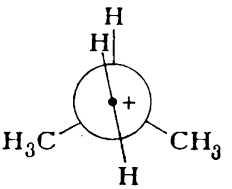
| | R | R′ | ΔF′, kJ/mole | Preferred conformations | |
|---|---|---|---|---|---|
| 1. | $C_2H_5$ | H | 27±2 |  | (total 67%) |
| 2. | $C_2H_5$ | $C_2H_5$ | 45±2 |  | (total 67%) |
| 3. | $C_6H_5$ | H | 28±2 |  | (>90%) |
| 4. | $C_6H_5$ | $C_6H_5$ | 34±1 |  | (ca. 64%) |

Apart from numerous data on the conformations of alkanes, information is now published in the literature on the conformational features of alkyl cations (8). Thus, the preferred conformations of alkyl, propyl, and isobutyl cations are the following (the thickened line in the formulas indicates the bond along which the conformation is represented):

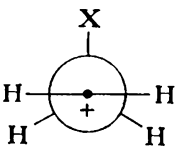




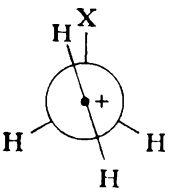




The preferred conformations and stabilization energies have been estimated and experimentally determined for a number of substituted alkyl cations:



IV



V

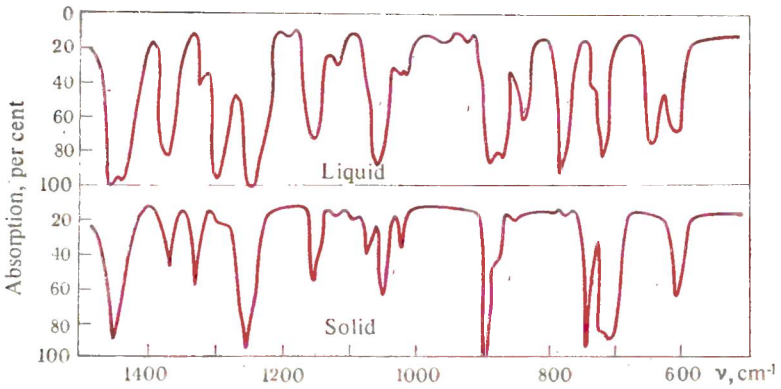
Conformation IV is preferable with $X = CH_3$, and conformation V if X = F, OH, CN; with X = H (the ethyl cation) both conformations are valid. The stabilization energy increases, as should be expected, with increasing number of alkyl groups at the cationic centre: the stabilization energy is 25-35 kJ/mole for $R—\overset{+}{C}H_2$, about 90-110 kJ/mole for $R—\overset{+}{C}H—R$, and about 170 kJ/mole for $(CH_3)_3C^+$.

The EPR spectra of radicals generated by γ-irradiation at a low temperature from halogen derivatives and incorporated into the channels of urea crystals point to hindered rotation (9).

## 4.2. CONFORMATIONS OF HALOGENOALKANES

With appearance of non-carbon substituents the estimation of the stability of conformers becomes complicated: it is now necessary to take into

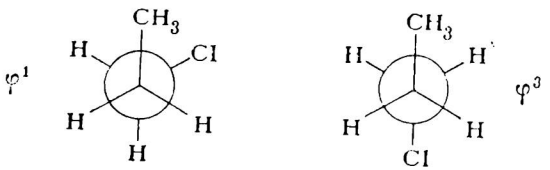
Figure 4.2.




*The IR spectra of propyl chloride in the liquid and solid states.*

account not only the volume of the substituents but also their specific interaction. The last-named factor begins to reveal itself even in the simplest monohalogen derivatives as the interaction of a methyl group with a halogen atom.

We shall begin our consideration with the simplest compound of this type, propyl chloride, $CH_3—CH_2—CH_2—Cl$. This compound can in principle exist in two conformations of differing energy—the skew and transoid (anti) conformations:




There is, of course, a third conformation, $\varphi^5$, but since we are speaking her of the *energy* of conformations and of the probability of their existence, the two skew conformations are indistinguishable (equivalent). For the skew conformations, we have only to take into account the statistical factor 2, i.e, the doubled probability of their appearance (other conditions being identical) as compared with the transoid (anti) conformation; this is important in entropy calculations.

In 1955, Pentin and Tatevsky (10), using the IR spectra, carried out a detailed study of the rotational isomerism of propyl chloride and bromide, *n*-butyl bromide, and isoamyl bromide. Upon transition from

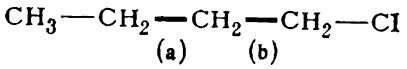
the liquid to the solid state the spectra of the compounds are strongly simplified (for propyl chloride, see Fig. 4.2). This is connected with the fact that in the crystalline state the compounds in question exist exclusively in the transoid conformation. A second, skew conformer appears in the liquid state. The last conformer was found to be *more stable* in the liquid and gaseous states than the transoid conformer. Thus, instead of a simple repulsion of the bulky groups, some other factor is operating in these compounds, which contributes to the *approach* of the hydrocarbon radical and the halogen atom. This factor may be the attraction of the dipoles of the C—halogen and $C—CH_3$ bonds (see also below).

The subsequent investigations conducted by other methods (electron diffraction method, the method of microwave spectra, etc.) have confirmed the assumption that the skew conformation is by 2.5 kJ/mole more favourable than the transoid conformation. Detailed information has been obtained (11) on the geometry of the propyl chloride molecule; it has been shown, in particular, that the dihedral angle between $CH_3$ and Cl in the skew conformation somewhat exceeds the normal angle, being equal to 65-70°; the valence angles and bond lengths are normal.

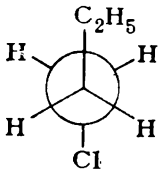
A model has been proposed for substantiation of some preferableness of the skew conformation (12). In this model, the intramolecular forces operating between the non-bonded atoms or groups may be likened to the interaction of the corresponding atoms *not* linked to one another within a single molecule. For example, the interaction between two fluorine atoms in 1,2-difluoroethane are compared in the model under consideration with the van der Waals interaction of two atoms of neon, a noble gas, an element next to fluorine in the Periodic System of the Elements. Why is it compared just with neon? It is because neon is close to fluorine in volume, and in the bound state fluorine has the electron shell of neon. The interaction between two chlorine atoms is tantamount to the interaction of two atoms of argon, and that between two bromine atoms, to the interaction of two atoms of crypton, and, finally, the interaction between two iodine atoms is likened to the interaction of two atoms of xenon. The energy of a number of halogen derivatives has been calculated on the basis of this model; the electrostatic interaction has also been taken into account. The results of the calculations have been found to be close to the data obtained by experiment.

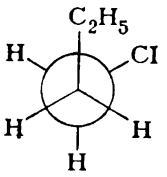
In going from propyl halides to the next homologues, 1-halobutanes, one has to consider conformations around *two* bonds (in the same manner as has been done for *n*-pentane). One transoid and two skew conformations are possible for two bonds. Since the two last-named conformations do not differ energetically and constitute a pair of antipode conformations, it will suffice to examine one of the skew conformations.

Thus, we have (again the thickened lines indicate bonds along which the conformations are represented):



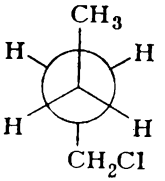

Conformations about bond (b)



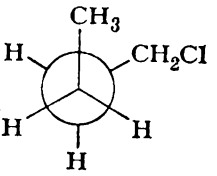




More stable
(by 1.3 kJ/mole)

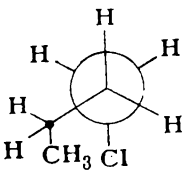
Conformations about bond (a)




More stable
(by 1.7 kJ/mole)



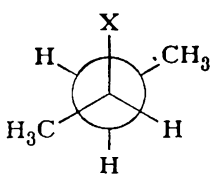

It is particularly interesting that in the conformational equilibrium there is present a noticeable amount (24 per cent) of the twice skew form with the chlorine atom being at a minimum separation from the methyl group:



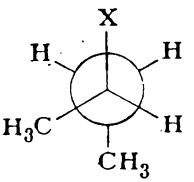

The relative stability of this conformation again leads us to assume that the forces of attraction rather than those of repulsion are operating between the chlorine atom and the methyl group.

The conformational equilibrium of 2-halobutanes has been studied by IR spectroscopy (13); the following data have been obtained on the con-

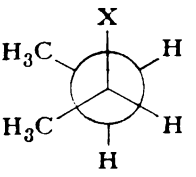
tent (in molar fractions) of the conformers (note that here all the three staggered conformations are different!):




VI




VII

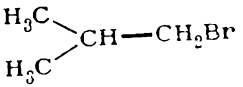


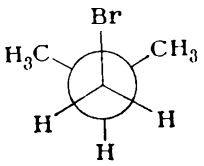

VIII

| | | | | |
|---|---|---|---|---|
| X=Cl | 0.67 | 0.18 | 0.15 | (gas phase) |
| | 0.56 | 0.27 | 0.17 | (liquid) |
| X=Br | 0.58 | 0.25 | 0.17 | (gas phase) |
| | 0.56 | 0.23 | 0.21 | (liquid) |

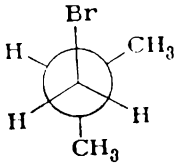
Using also the IR spectra of 2-halobutanes, the authors of another work (14) came to the conclusion that conformation VIII is the preferred conformation in crystals.

Halogen derivatives with a branched carbon chain have their own specific conformational features. For example, there exist two conformations for isobutyl bromide:




IX



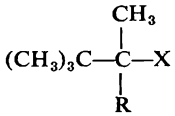

X

A study of the IR spectra of this compound in the liquid and crystalline states has shown that the spectra are almost the same in the two states of aggregation. This is an indication either of the existence of the compound only in one of the conformational forms or of the closeness of the relative stabilities of both conformers. No final choice between these two possibilities has been made. The study of the conformation of a related compound, isobutyl chloride, has provided a more definite result

(15). It has been established that of the two possible conformations the transoid-skew conformation (analogous to conformation X, with chlorine in place of bromine) predominates (80 per cent).

This result was somewhat unexpected since from what has been said above about the conformations of propyl chloride it might be expected that conformations of the IX type with two favourable $CH_3$-Cl interactions would be preferred. This contradiction was explained with account taken of the fact that the dihedral angle for a conformation of the type X appeared to be somewhat too high (66°), as was noted earlier for propyl chloride. Probably, this angle provides a favourable disposition of the methyl group and the chlorine atom relative to each other. In a conformation of the type IX the two $CH_3$ groups cannot be at such an angle (having occupied a favourable position relative to one of the $CH_3$ groups, the chlorine atom will be too close to the second $CH_3$ group), which is what renders a conformation of the IX type less favourable.

A large group of compounds having the general formula



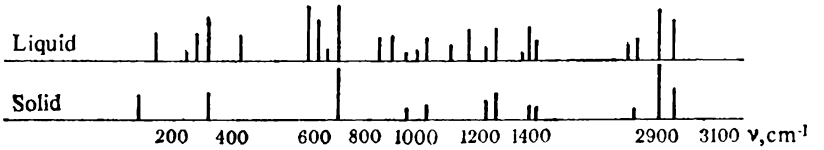
have been studied by English authors with the aid of the NMR method (16). The values of the potential energy barrier to rotation about the $(CH_3)_3C$—C bond obtained for such compounds are presented in Table 4.3.

TABLE 4.3

| R | X | $\Delta G^{\neq}$, kJ/mole | R | X | $\Delta G^{\neq}$, kJ/mole |
|---|---|---|---|---|---|
| H | Cl | 35.0 | $CH_3$ | I | 46.7 |
| $CH_3$ | H | 29.3 | $C_2H_5$ | Cl | 45.4 |
| $CH_3$ | F | 33.8 | *tert*-$C_4H_9$ | Cl | 48.0 |
| $CH_3$ | Cl | 44.0 | $CH_2C_6H_5$ | Cl | 45.5 |
| $CH_3$ | Br | 44.9 | $C_6H_5$ | Cl | 42.6 |

To sum up, it should be emphasized once again that not only forces of repulsion and steric hindrances exist between the substituents but there may also develop forces of attraction which are responsible for the existence of the corresponding conformations.

Figure 4.3.




*The Raman spectrum of* 1,2-*dichloroethane.*

## 4.3. CONFORMATIONS OF DI- AND POLYHALOGENOALKANES

Numerous data are available on the conformations of compounds containing two halogen atoms. The foundations of the conformational analysis of aliphatic compounds were laid exactly in the investigations of compounds such as 1,2-dihaloethanes. The existence of a conformational equilibrium is evidenced here, in particular, by Raman and IR spectral data, the analysis of which is facilitated due to the smaller number of atoms in the molecule as compared, say, with butane.

In a general case, for a three-dimensional molecule consisting of $n$ atoms, there must be not more than $3n-6$ lines in the Raman spectrum, which corresponds to the number of normal vibrations possible for the molecule. The spectrum of solid dichloroethane shows a smaller number of lines than that of dichloroethane in the liquid state (Fig. 4.3); the extra lines appearing upon transition to the liquid state are due to the contribution of new conformers.

An important role in the study of the conformations of halogen derivatives and other compounds containing several polar groups is played by the method of dipole moments. This method has also been successfully used in the investigation of 1,2-dihalogenoethanes. In the case of the transoid conformation of 1,2-dichloroethane (XI) the dipole moment is equal to zero because of the cancelling of the dipoles of the C—Cl bonds on vector addition. The dipole moment calculated for the skew form (XII) is about 3.2D.

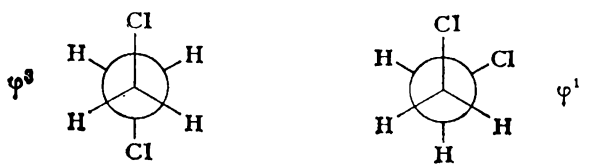
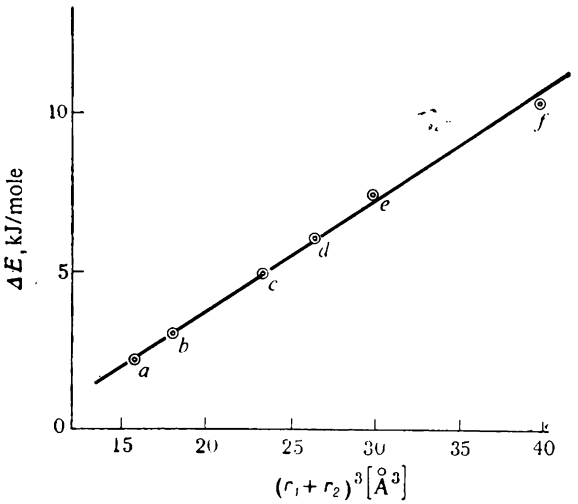


Figure 4.4.




*The conformational free energy of* 1,2-*dihaloethanes versus the size of the interacting halogen atoms:*

*a* — *data for* 1,2-*fluorochloroethane; b* — 1,2-*fluorobromoethane; c* — 1,2-*dichloroethane; d* — 1,2-*chlorobromoethane; e* — 1,2-*dibromoethane; f* — 1,2-*diiodoethane.*

The experimentally determined dipole moment of 1,2-dichloroethane depends on temperature: it equals 1.12D at +32°C and 1.54D at +270°C. Using these data, it is easy to find, through calculations, that in the vicinity of room temperature the fraction of the transoid form is approximately 2/3, and that near 300°C both conformations become equally probable.

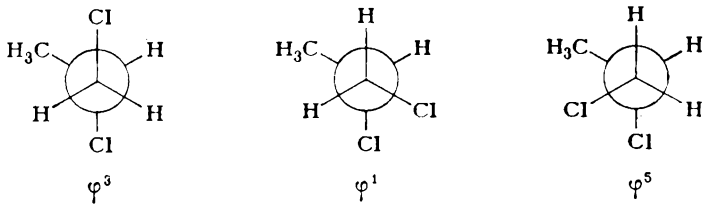
The same results have been obtained in the study of the conformations of 1,2-dibromoethane, 1,2-diiodoethane and the perfluorated analogue of the latter compound. For example, in the case of 1,2-dibromoethane in the gaseous state, the energy difference between the skew and transoid conformations is about 5.9 kJ/mole. At room temperature, there is 85 per cent of the transoid and 15 per cent of the skew conformation in the equilibrium. Upon transition from the gaseous to the liquid state the dielectric constant of the medium increases and therefore the electrostatic repulsion of the dipoles of the C—Br bond in the skew conformation decreases. This lowers the energy difference between the two forms

down to 3 kJ/mole and leads to the 35 per cent increase of the population of the skew form.

The results of the conformational studies of 1,2-dihaloethanes have been summed up (17) in the form of a rule which establishes the dependence of the conformational energy (the energy difference between the skew and transoid conformations) on the total volume of the interacting halogen atoms involved (Fig. 4.4). This dependence was obtained by using data referring to the gaseous state of dihaloethanes. In the liquid state and in solutions the energy varies noticeably. This can easily be explained: an important part is played here by electrostatic interaction, which depends on the dielectric constant of the medium.

Thus, for example, the study of the IR spectra of 1,2-chlorofluoroethane and 1,2-bromofluoroethane (18) has shown that different conformations predominate in different states of aggregation: the skew conformation is more stable in the liquid phase ($\Delta E$ ca. 3.8-4.2 kJ/mole), and the transoid conformation in the gaseous phase ($\Delta E$ ca. 0.8-1.3 kJ/mole). In this case too, the conformational equilibrium in the liquid phase is influenced by intermolecular forces but, in the opinion of the authors of the work under consideration, these forces do not reduce to the simple weakening of the dipole-dipole repulsion mentioned above. An analogous result has been obtained by the study of 1,2-fluoroiodoethane.

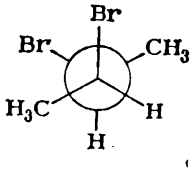
As a further example, let us consider 1,2-dichloropropane, for which there may exist three staggered conformations:



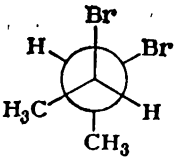

In the $\varphi^5$-conformation all the three substituents and in the $\varphi^3$- and $\varphi^1$-conformations only two substituents are brought closer to one another. The first of these conformations (with two pairs of skew interactions) must have a noticeably greater energy than the two others, and therefore its participation in the conformational equilibrium is minimal. Thus, 1,2-dichloropropane should be expected to exist mainly as an equilibrium mixture of two conformations. This conclusion has been supported by the study of the Raman spectra.

The conformational equilibrium of the DL-diastereomer of 2,3-dibromobutane is characterized by the following data (the numerals indicate

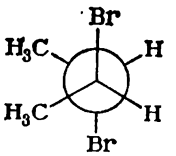
the content of conformers expressed in molar fractions at room temperature) (13):




0.35



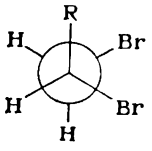

0.15



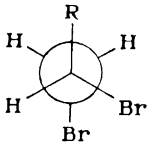

0.50

2,3-Dibromo-2-methylbutane in a solution of carbon tetrachloride exists by 86 per cent in a conformation with the transoid arrangement of bromine atoms (20).

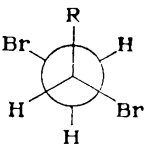
Of the compounds with a more complex carbon skeleton only compounds of the type R—CHBr—$CH_2$Br (where R = *tert*-butyl or phenyl) have been studied (19). The following conformations are possible for such compounds:




$\varphi^5$



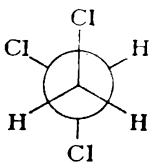

$\varphi^1$



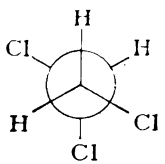

$\varphi^3$

For the same reasons that have been mentioned in the consideration of 1,2-dichloropropane, the $\varphi^5$-conformation is considerably less favourable than the two others. And the relative stability of the conformations $\varphi^1$ and $\varphi^3$ depends on the nature of the substituent: if R = *tert*-butyl group, the $\varphi^1$-conformation is preferred; if R is phenyl, the $\varphi^3$-conformation predominates. This is one of the numerous examples demonstrating that the phenyl group does not avoid neighbourhood with other substituents, in spite of its considerable bulkiness.

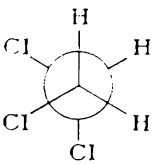
We shall begin our consideration of the conformational features of polyhaloalkanes with 1,1,2-trichloroethane, for which the following three different conformations may be written:




XIII



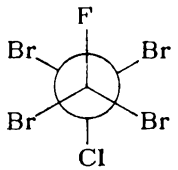

XIV



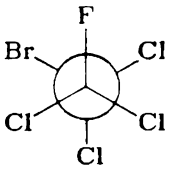

XV

The form XV may be neglected for the reasons that have already been discussed, and the remaining two conformations are mirror-image conformations and are therefore indistinguishable in energy, i.e., the compound under consideration must have only one rotational isomer. The fact that the dipole moment in this particular case is independent of temperature has been interpreted as a confirmation of this conclusion.

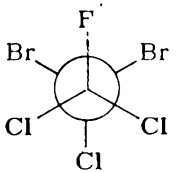
Goursot-Leray and Bodot (21) compared the values of the potential energy barrier to rotation calculated in accordance with the Westheimer model with those found experimentally for the various chloro-substituted derivatives of ethane, containing one to six chlorine atoms. As the number of halogen atoms increases the potential energy barrier gradually increases from 15.5 kJ/mole for ethyl chloride to 46-59 kJ/mole for hexachloroethane. In contrast, in analogous compounds with fluorine atoms in place of hydrogen atoms (22) the potential barriers are almost independent of the number of chlorine or bromine atoms, being equal to 14-18 kJ/mole. We shall not consider the relevant works in detail; only the preferred conformations of some compounds of the given series are given here:



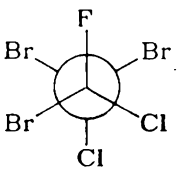

1-Fluoro-2-chloro-tetrabromoethane




1-Fluoro-2-bromo-tetrachloroethane




1-Fluoro-2,2-dibromo-trichloroethane

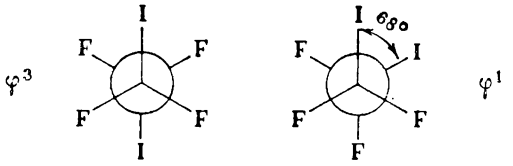



1-Fluoro-1,2-dichloro-tribromoethane

These compounds are all characterized by the skew position of fluorine atoms relative to bromine atoms. The NMR method used for conformational studies also indicates the considerable stability of such conformations: the conformational free energies in this series range from 42 to 63 kJ/mole (23). The energies of the skew and transoid conformations differ insignificantly for 1,1,2,2-tetrabromoethane (24).

In the case of 1,2-diiodotetrafluoroethane, the IR spectral data point to the presence of the transoid and skew conformers with an energy

difference of the order of 7.6 kJ/mole. The dihedral angles have also been calculated for both conformations, as a result of which it has been established that this angle somewhat exceeds the normal value in the skew conformation (25):

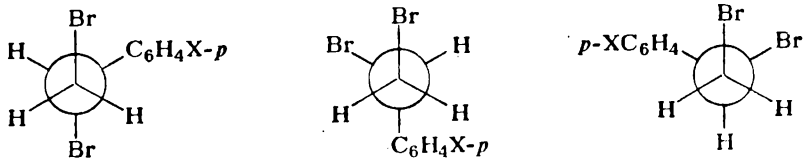



Di- and polyhaloalkanes with a larger number of carbon atoms have been studied, the following compounds being taken as examples: 1,1,2,2-tetrachloropropane (26), halogenated dimethylbutanes (27), and halogenophenylalkanes. These compounds may exist in two stereoisomeric forms (*erythro-* and *threo*-diastereomers); each of the stereoisomers has its own preferred conformations. For more detail, see Sec. 4.7.

Infrared and nuclear magnetic resonance spectroscopy indicates the existence of nine conformers for 1,2,3-trichloropropane.

Compounds of the type $BrCH_2$—CHBr—$C_6H_4X$-*p* have been used as convenient models for estimating the electrostatic effect of polar substituents on the conformation of compounds since the substituent X, which is in the *para*-position in the benzene ring has no effect on the *steric* interaction of the phenyl group with other substituents and only changes the nature of the dipole (28).

Of the three possible conformations shown below the first one is the most favourable (according to steric considerations and dipole-dipole interaction):




All the compounds mentioned so far have vicinal halogen atoms. Of the compounds with halogen atoms more remote from each other, only 1,4-dichlorobutane and 1,4-dibromobutane have been studied (29). The $HalCH_2$ groups are in the transoid position to one another in these compounds.

## 4.4. CONFORMATIONS OF OTHER SUBSTITUTED ALKANES

An important work was accomplished in 1967 by Whitesides and coworkers (30), who studied the conformational features of various mono-

substituted 3,3-dimethylbutanes. Two conformations, namely, a transoid and a skew conformation, can be built about the central C—C bond:

$$(CH_3)_3C-CH_2-CH_2-X$$

XVI

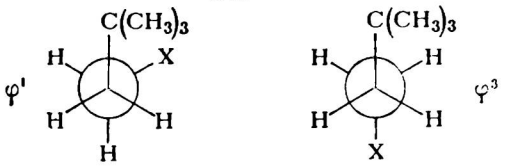
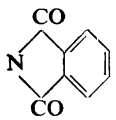



TABLE 4.4. THE CONFORMATIONAL ENERGIES OF VARIOUS SUBSTITUTED 3,3-DIMETHYLBUTANES XVI

| Substituent X | ΔE kJ/mole | ΔE kcal/mole | Substituent X | ΔE kJ/mole | ΔE kcal/mole |
|---|---|---|---|---|---|
| $S(CH_3)_3$ | 15.5 | 3.7 | HgCl | 4.87 | 1.16 |
| $AlR_2 \cdot p(C_2H_5)_2O$ | 10.1 | 2.4 | COOK | 4.87 | 1.16 |
| $MgR \cdot p(C_2H_5)_2O$ | 9.2 | 2.2 | $NH_2$ | 4.83 | 1.15 |
| $P(C_6H_5)_2$ | 8.34 | 1.99 | $N(CH_3)_2$ | 4.70 | 1.12 |
| $ZnR \cdot p(C_2H_5)_2O$ | 7.13 | 1.7 | Cl | 4.53 | 1.08 |
| $C_6H_5$ | 6.93 | 1.65 | COOH | 4.48 | 1.07 |
| $-\overset{+}{N}H(CH_3)_2\ \bar{S}O_3H$ | 6.93 | 1.65 | COCl | 4.32 | 1.03 |
| I | 6.76 | 1.61 | NHCHO | 4.23 | 1.01 |
| $CD_2OH$ | 6.58 | 1.57 | $COOCH_3$ | 3.70 | 0.98 |
| $-\overset{+}{N}H_3\ \bar{S}O_3H$ | 6.50 | 1.55 | CN | 3.49 | 0.83 |
| SCN | 6.29 | 1.50 | OH | 3.07 | 0.73 |
| $SC_6H_5$ | 6.21 | 1.48 | $CH_3$ | 2.94 | 0.70 |
| $SCH_3$ | 6.16 | 1.47 | $OC_6H_5$ | 2.5 | 0.6 |
| Br | 5.49 | 1.31 | $OSO_2C_6H_4Br$-*p* | 2.5 | 0.6 |
| $CONH_2$ | 5.37 | 1.28 | F | 2.5 | 0.6 |
| HgR | 5.28 | 1.26 | H | 0.00 | 0.00 |
|  | 5.00 | 1.19 | | | |

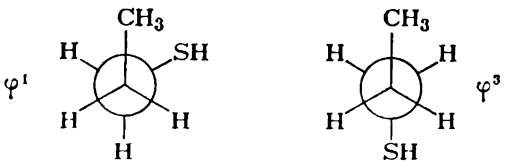


The energy difference $\Delta E$ between the two conformations $\varphi^1$ and $\varphi^3$ has been determined on the basis of NMR spectral data for compounds with different substituents (Table 4.4). The nature of the conformational

energy in this case is the magnitude of the skew interaction of the *tert*-butyl group with the corresponding substituent.

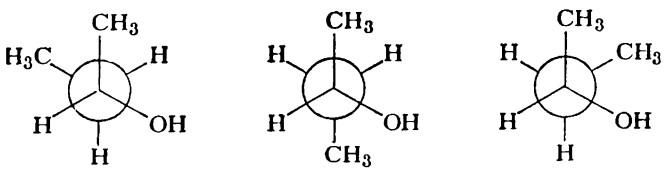
Analysis of the values given in Table 4.4 will clearly show that the conformational energy is influenced not by the entire volume of the substituent but by the volume of that part of it which is nearest to the conformational axis (the so-called **effective size**). Thus, the conformational energies for three sulphur-containing groups, SCN, $SCH_3$, and $SC_6H_5$, are practically equal, though their volumes are substantially different. But the effective volume in all the three cases is the same volume of the sulphur atom. Sometimes, even substituents with a large effective volume do not give high conformational energy; this refers, for example, to the HgCl group. This once again draws our attention to the fact that not only the mere steric effect, not only the volume, but the nature of the groups is also important in conformational studies. The low conformational energy in the case of mercury derivatives is believed to be due to the easy deformability of the electron shell of mercury.

Of the derivatives of propane only propane-1-thiol has been studied; the possible conformations of this compound are as follows:




In the crystalline state, this compound exists entirely in the anti (transoid) conformation; on melting there appears a certain fraction of the skew conformation (31).

The study of the conformational equilibrium of 2-butanol is of interest as an example of the use of a method which has not yet been mentioned in this book—the investigation of the temperature dependence of the optical rotation of the optically active form of this compound. The following data on the conformational equilibrium have been obtained:




XVII 41.3%

XVIII 42.3%

XIX 15.3%

As has repeatedly been pointed out, conformation XIX is less favourable because all the three substituents are very close to one another. The conformations XVII and XVIII are equally probable since the skew $CH_3$-$CH_3$ and $CH_3$-OH interactions are energetically nearly equivalent (see also the conformational energies of these groups in Table 4.4).

In 1-butanol, there may appear various conformations due to the rotation about a number of bonds. Estimations of the fraction of the transoid and skew conformations around each of the bonds have been reported in the literature (32):

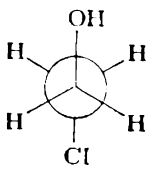
| | $CH_3-CH_2-CH_2-CH_2-O-H$ | | |
|---|---|---|---|
| The fraction of the transoid conformation, % | 99.7 | 46 | 45 |
| The fraction of the skew conformation, % | 0.3 | 54 | 55 |

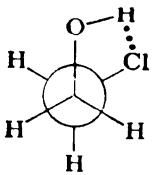
Using the NMR method and introducing deuterium as a label, Snyder (33) studied the conformational equilibrium of 3-phenyl-1-propanol; the skew and transoid conformations about the $C_1$—$C_2$ and $C_2$—$C_3$ bonds were found to be approximately equally probable.

In the case of alkanes containing two different functional groups, it is especially important to take into account not only the volume but also the specific interaction of groups. For instance, with β-halopropionitriles of the general formula

$$X—CH_2—CH_2—CN \qquad X = F, Cl, Br, I$$

the conformation more stable in the liquid phase is the skew conformation, which might seem to be unfavourable for the purely steric considerations (34). The situation is analogous with ethylene chlorohydrin, of the two possible conformations of which the skew conformation is favourable because of the formation of a hydrogen bond between the hydroxyl group and the chlorine atom (the gain of energy is of the order of 15 kJ/mole) (35).

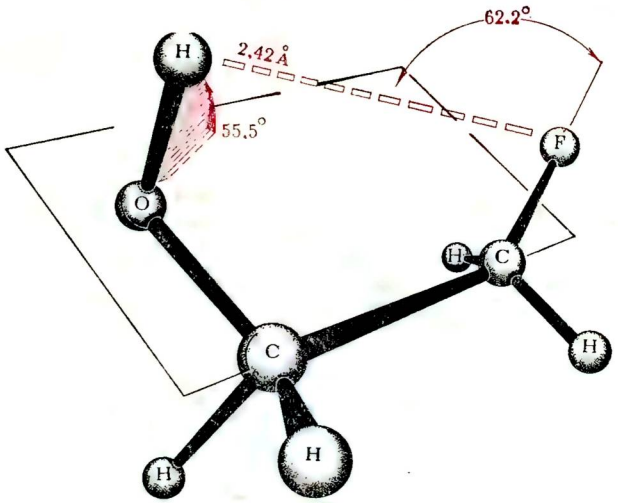


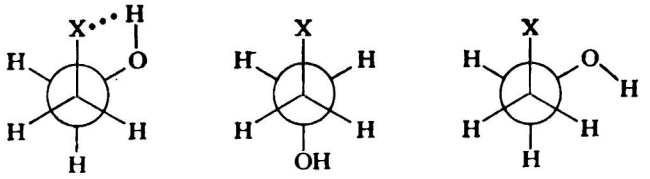

It may seem that the eclipsed $\varphi^0$-conformation of ethylene chlorohydrin provides the most favourable conditions for the formation of a hydrogen bond (the closest disposition of the interacting groups). Examina-

tion of the geometry of the molecule with account taken of the atomic radii, however, shows that this is not actually the case: in the $\varphi^0$-conformation the groups are so close to one another that steric hindrances arise, which make it impossible for the atoms to be arranged at ordinary valence angles with the bond length being normal.

Because of the formation of a hydrogen bond, 2-fluoroethanol (the fluorine analogue of ethylene chlorohydrin) also exists almost exclusively in the skew conformation, the geometrical parameters of which are given below (36):

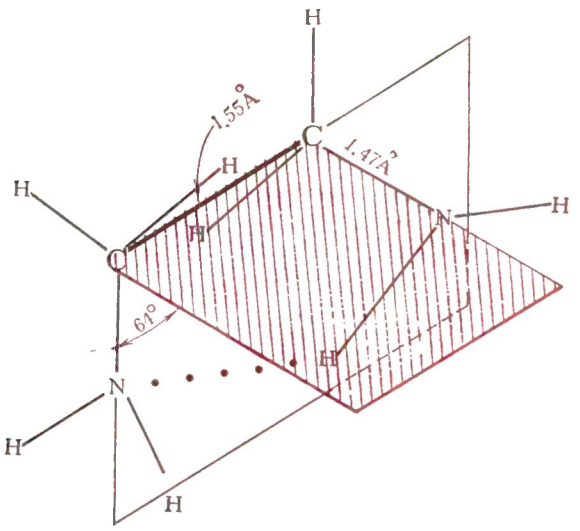



The situation is analogous with 2-bromoethanol and 2-cyanoethanol (37). It is believed (38) that the conformational equilibrium in compounds of this kind involves three conformers: a skew conformer with a hydrogen bond, which is the most stable; a transoid conformer; and a skew conformer containing no hydrogen bond, which is the least favourable of them all:



In the case of 2-nitroethanol, in the solid, liquid, and vapour states there coexist the transoid and the skew form; the latter is stabilized by a weak intramolecular hydrogen bond. At the same time, the low volatility of 2-nitroethanol (b.p. 198°C) as compared with 2-bromoethanol (b.p. 150°C) and 2-chloroethanol (b.p. 129°C) is an indication that the manifestation of the formation of an *intermolecular* hydrogen bond in 2-nitroethanol is sufficiently strong (39).

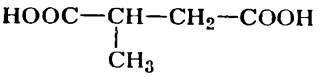
The intramolecular hydrogen bond is also responsible for the predominance of the skew conformation in gaseous ethylenediamine, the geometrical parameters for which have been found by the electron diffraction method (40):

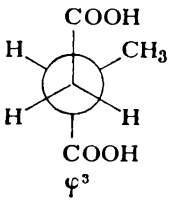



Some compounds which are explicitly incapable of forming a hydrogen bond nevertheless exist preferably in the skew conformation; one example is 1,2-dimethoxyethane (41). Some authors (42) ascribe this, even in the case of 2-haloethanols, to the effect not of the hydrogen bond but of the dipole-dipole interaction alone.

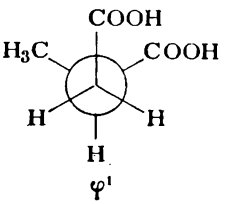
Of the two energetically different conformers of succinic acid, HOOC—$CH_2$—$CH_2$—COOH, the transoid (anti) conformer is preferred (according to the NMR spectral data). In going to the nearest homologue, methylsuccinic acid, one has to consider the possible appearance of *three* energetically non-equivalent conformers because of the lower symmetry

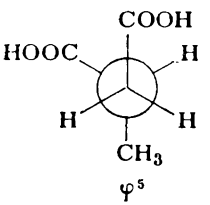
of the molecule. The transoid form is the most favourable conformer in this case too (43):





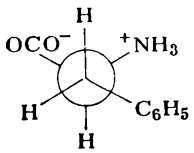
Transoid (anti)

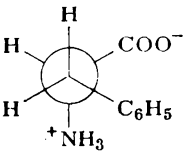


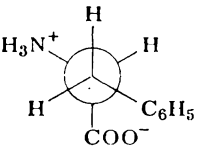


Skew (gauche)

In the case of phenylalanine, $C_6H_5—CH_2—CHNH_2—COOH$, there are also three non-equivalent conformations possible. The NMR spectra show that they all participate in the conformational equilibrium:

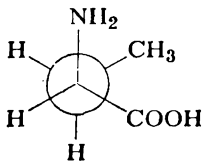




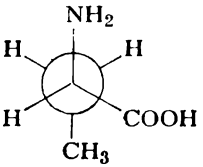


The ratio of these conformers is especially strongly dependent on the nature of the solvent, concentration and temperature (44).

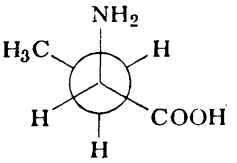
Interesting results have been obtained in the investigation of the conformation of α-aminobutyric acid. This compound is known to exhibit dimorphism—the ability to exist in two different crystalline forms (45). It has been established, by means of X-ray structure analysis, that these crystalline forms differ in the conformations of the molecules making up the crystals. There are three such conformations:



XX



XXI

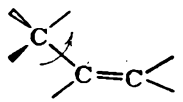


XXII

Whereas crystals of one form contain all the three conformers, crystals of the other form consist exclusively of molecules in conformation XXII. The conformation XX is preferred in aqueous solution.

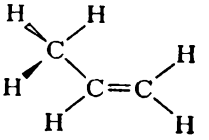
## 4.5. CONFORMATIONS ABOUT BONDS INVOLVING CARBON ATOMS IN A STATE OF $sp^2$-HYBRIDIZATION

In all the examples of the conformational equilibrium considered above, we were speaking of rotational isomers about the bond between two tetrahedral carbon atoms (in a state of $sp^3$-hybridization). At the same time, there are many compounds for which one has to deal with conformations about bonds involving a trigonal carbon atom (in a state of $sp^2$-hybridization). Examples are olefins, in which one tetrahedral carbon atom and one trigonal carbon atom are involved in the formation of conformers about one of the bonds:

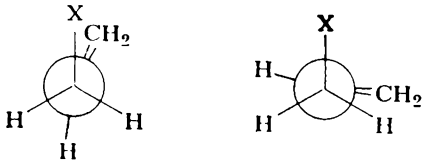


The geometry of such a grouping makes one of the substituents at the tetrahedral carbon atom be in the eclipsed position to the substituent at the trigonal carbon atom.

The rotation of the $CH_3$ group in propylene leads to the formation of the most stable conformation in which one of the hydrogens of the $CH_3$ group lies in one plane with the ethylene system (46), i.e., is eclipsed by it.



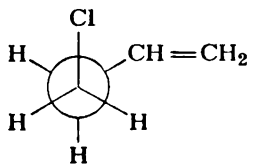
For allyl halides, $CH_2{=}CH{-}CH_2X$, there have been detected two conformers with the aid of microwave spectra, the skew form being somewhat more stable (47).



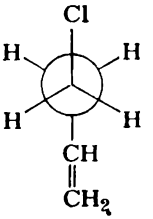

Fully eclipsed (cisoid) Skew

The NMR method has been used to study the conformations of stereoisomeric *cis*- and *trans*-1,3-dichloropropenes; the skew conformer was found to be more stable in this case too (in the Newman formula given above, the CHCl group in place of the $CH_2$ group) (48).

The examination of the IR spectra of 4-halobutenes having the structure $CH_2{=}CH{-}CH_2{-}CH_2X$ has shown that here too the skew conformer XXIII is more stable than the transoid conformer XXIV (49), the entire carbon chain being planar:




XXIII



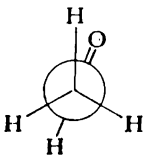

XXIV

The problems of the conformation about the bond between the tetrahedral and trigonal carbon atoms also arise in the case of carbonyl and carboxyl compounds.

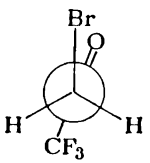
**Acetaldehyde** (50) exists in a conformation with the oxygen atom being eclipsed by a hydrogen atom (conformation XXV).

It is believed that this is the result of the attraction of the partial charges $O^{\delta-}$ and $H^{\delta+}$. The conformation in which the oxygen atom is eclipsed by a methyl group has been confirmed for 2-butanone by electron diffraction studies (51).

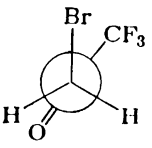
Symmetrical difluoroacetone, $FCH_2{-}CO{-}CH_2F$, exists in two equally probable eclipsed conformations (52), while with 1,1,1-trifluoro-3-bromoacetone (53) the ratio of the forms XXVI and XXVII is about 4:1.




XXV



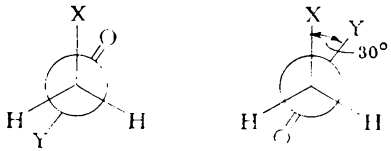

XXVI



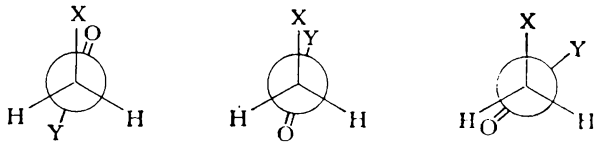

XXVII

A great number of works have been devoted to the study of the conformations of acid halides of haloacetic acids. A conclusion was drawn in one of the first works, on the basis of IR and Raman spectra, that

these compounds in the vapour and liquid states exist in two conformations:




In the second of the conformations presented above, the dihedral angle between X and Y is about 30°, i.e., the form is intermediate between $\varphi^0$ and $\varphi^1$. Later, three conformations were considered to be possible (54):




Transoid Cisoid Skew

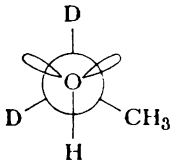
In the case of monofluoroacetic acid (X = F; Y = OH), the transoid conformation prevails, its fraction in the equilibrium being about 70 per cent ($\Delta G = 2.7 \pm 0.1$ kJ/mole, the barrier to rotation about the C—C bond is about 24 kJ/mole). The conformations of the enolate anions formed by acetoacetic ester and other β-dicarbonyl compounds have also been studied (55).

## 4.6. CONFORMATIONS ABOUT CARBON-HETEROATOM BONDS

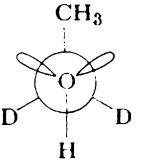
The preceding sections were concerned with conformations about carbon-carbon bonds. But even in the simplest compounds of the type R—$CH_2$——$XH_n$ there arise conformational problems of a different kind: different conformations may exist at the C—X bond, where X is the atom of oxygen, sulphur, nitrogen or of some other polyvalent element. A characteristic feature of such atoms is the presence of free electron pairs. These electron pairs are of importance in the consideration of preferred conformations.

We shall begin with a simple case of deuterated ethyl alcohol, $CH_3$——$CD_2$—OH. The more favourable of the two conformations possible for it is the form XXIX (56) (here and further in the text, the free elec-

tron pairs of atoms in the conformations of such compounds are denoted by loops):




XXVIII




XXIX

Data on the conformations of a number of alcohols have been obtained with the aid of NMR spectroscopy (57). The spin-spin coupling constants of the protons of CH—CH depend on the distance between them: it is 2 cps for the skew arrangement ($J_{skew}$) and 12 cps for the transoid arrangement ($J_{trans}$). The observed constant ($J_{obs}$) for ethyl alcohol is 5.1 cps. The following equation widely used for calculations in such cases has been employed ($p_A$ and $p_B$ are the molar fractions of the conformers):

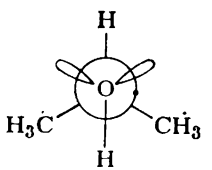
$$J_{obs} = p_A J_{trans} + p_B J_{skew}$$

The ratio of the conformers of the types XXVIII and XXIX (provided that hydrogen atoms are substituted for the deuterium atoms) calculated by this equation is equal to about 70:30. This result is not consistent with the above-mentioned preference of conformation XXIX for the deuterated alcohol. Since the barrier to rotation about the C—O bond in alcohols is very low (it is only 3.4-4.7 kJ/mole), it is possible that even the replacement of hydrogen by deuterium will change the ratio of the conformers.

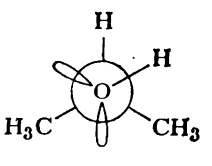
The following data on the ratio of the conformations around the C—O bond have been obtained for other alcohols:

(1) For isopropyl alcohol:

$(CH_3)_2CH—OH$

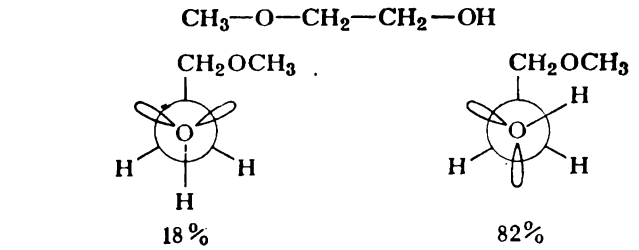



23%

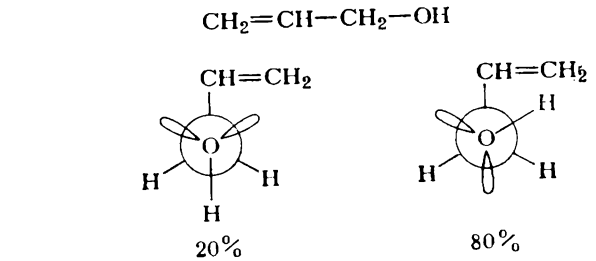



77%

(2) For the monomethyl ether of ethylene glycol:

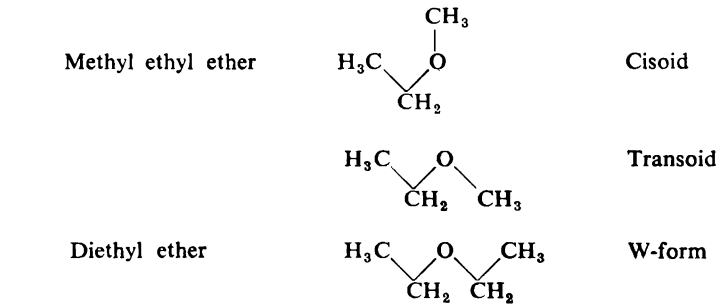



(3) For allyl alcohol:




Propargyl alcohol, CH≡C—$CH_2$—OH, has the same ratio of the conformers.

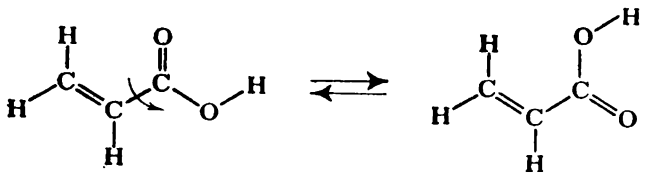
Hayashi and coworkers have detected the following conformations for ethers (58):



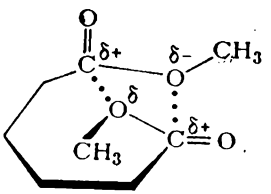

The rotation about the O—$CH_3$ bond in compounds of the type

X—CO—O—$CH_3$ X=H, $CH_3$, $CH=CH_2$, C≡CH, F, CN

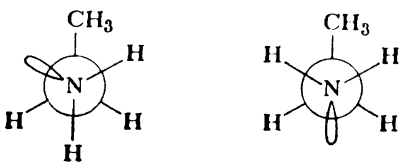
has also been studied (59): in the esters of formic, acetic, acrylic, propargylic, fluorocarbonic, and cyanocarbonic acids. For acrylic acid, two conformers around the C—O bond have been found, the first one being somewhat preferable (60):



In these cases, we are speaking of the conformations around the bond between two trigonal carbon atoms. Data have been published on conformations around the bond between oxygen and a trigonal carbon atom in esters and thioesters of mono- and dicarboxylic acids and in esters of carbonic acid (61). An interesting result has been obtained by these authors for the esters of adipic acid, which are prone to form a cyclic conformation due to the dipole-dipole interaction:

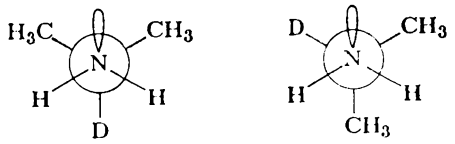


As to nitrogen-containing compounds we shall consider data on the conformations around the C—N bond in amines. Two conformations around the C—N bond are possible for ethylamine:



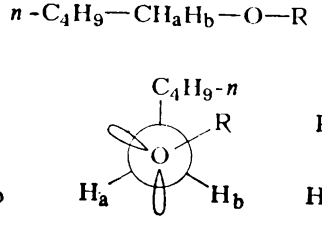
According to estimations (62), the second conformation with the transoid (anti) arrangement of the $CH_3$ group and a free electron pair is

more preferable. Of the two conformations of 2-deuteroisopropylamine, $CH_3—CD(NH_2)—CH_3$, the first conformation with the skew disposition of the $CH_3$ groups relative to the free electron pair of the nitrogen atom is more stable (63):




The value of the potential energy barrier to the rotation about the C—N bond may be rather high; for example, for *tert*-butyldimethylamine, $(CH_3)_3C—N(CH_3)_2$, the enthalpy of activation is $26 \pm 1$ kJ/mole (64). The conformation of diethylamine has also been investigated on the basis of IR spectra (65).

The conformational effects exert an influence not only on the spin-spin coupling constants, as has been noted above, but also on the position of signals in NMR spectra. Generalizing the evidence available, Price (66) formulated an empirical rule, according to which each free electron pair being in the skew position relative to a proton shifts the NMR signal of this proton by 1.7 ppm to the side of the weak field. The application of this rule may be illustrated by the shifts of proton signals in esters; for example:

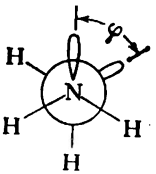
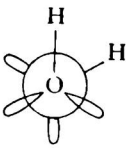
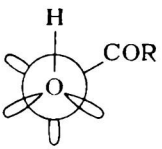
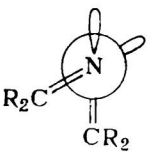
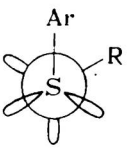



| Shift of protons under the influence of skew electron pairs, ppm | 1.7 | 1.7 | 3.4 | 1.7 | 1.7 | 3.4 |
|---|---|---|---|---|---|---|

If a compound has free electron pairs on adjacent atoms, these electron pairs tend to occupy the skew position to one another. A similar behaviour is displayed by free electron pairs that are in the vicinity of polar bonds. This phenomenon has come to be known as the **gauche effect**

(67). The manifestation of the gauche effect may be illustrated by th preferred conformations presented in Table 4.5.

TABLE 4.5

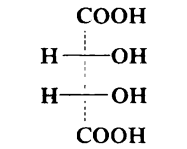
| Compound | Formula | Preferred conformation | Angle φ |
|---|---|---|---|
| Hydrazine | $H_2N-NH_2$ |  | 90–95° |
| Hydrogen peroxide | HO—OH |  | 111° |
| Peracids | $R-\underset{\underset{O}{\|}}{C}-O-O-H$ |  | 72 ± 4° |
| Azines | $R_2C=N-N=CR_2$ |  | 90–135° |
| Disulphides | Ar—S—S—R |  | 103° |

The preference of the skew conformations of 2-haloethanols, 1,2-dimethoxyethane and related compounds is also interpreted from the stand-

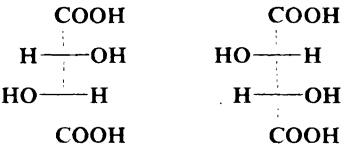
point of the gauche effect in the form of the skew interaction of free electron pairs with polar bonds (see page 244).

## 4.7. CONFIGURATIONS AND CONFORMATIONS OF DIASTEREOMERS

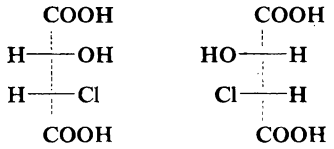
As we already know, compounds with several chiral centres are capable of existence in stereoisomeric forms which not only differ in studies carried out by means of a polarimeter but also have different physical constants. Such stereoisomeric forms are called diastereomers (or diastereoisomers). A special case of a pair of diastereomers is the *meso*-forms of compounds with two identical chiral centres and their racemic forms (capable of being resolved into optical antipodes). In a more general case, when there are two *non-identical* chiral centres, diastereomers are termed the *threo*- and *erythro*-forms:



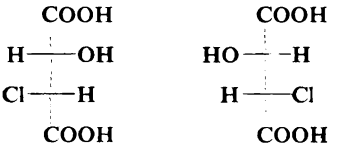

Mesotartaric acid




Racemic tartaric acid




*erythro*-Form of chloromalic acid
(a pair of optical antipodes)




*threo*-Form of chloromalic acid
(a pair of optical antipodes)

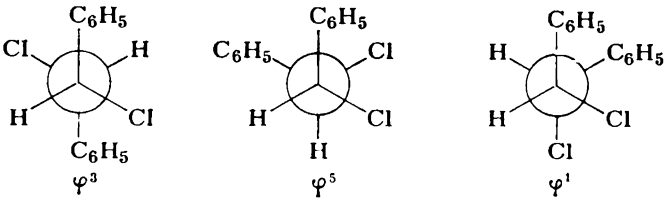
For further consideration it will suffice to compare the *meso*-form with *one* of the optical antipodes of the racemic form, or one antipode of the *erythro*-form with one antipode of the *threo*-form because everything that will be said about one antipode will be valid for the second.

The problem of determination of the configurations of diastereomers has already been treated in Chapter 3. Now we shall consider the conformational features of diastereomers. The main specific feature is as follows: each diastereomer has *its own* preferred conformations. It is the conformational differences between diastereomers that determine, in the long run, the differences in their physico-chemical properties.

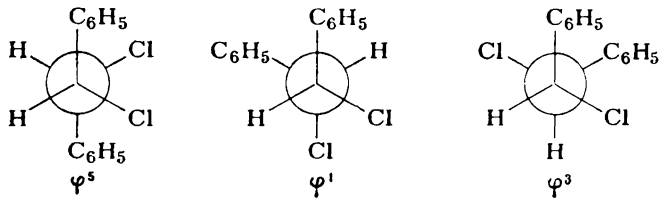
Let us first consider dichlorostilbene, $C_6H_5$—CHCl—CHCl—$C_6H_5$, which exists as two diastereomers—the *meso*-form and the racemate.

For each of the configurations there are, in principle, three conformations*:

Conformations of the *meso*-form




Conformations of the optically active form

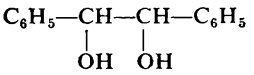



Since a confusion invariably arises in these questions, it will be useful to emphasize once again the following point: there are two different compounds, the *meso*-form of dichlorostilbene and its racemic form. These are really different compounds with different constants, and different properties. Either of these compounds is in fact a set of several conformational forms. Note also that here we deal not with two energetically different conformations, as has been the case with many of the examples so far considered, but with *three* conformations, the probability of existence of which is to be estimated.

The most favourable conformation of the *meso*-form is the transoid ($\varphi^3$) conformation since in the conformations $\varphi^1$ and $\varphi^5$ all the four substituents are arranged one after another and there is one skew interaction more than in the transoid form. The most favoured conformation of the other diastereomer is the conformation $\varphi^1$. Thus, we arrive at the conclusion that the preferred conformations for the *meso*-form and the racemic form (for which one antipode has been considered as a full representative) are different. How could this be checked? To answer this question, let us have a close look at the arrangement of the identical substituents in the preferred $\varphi^3$-conformation of the *meso*-form. The identical substituents occupy the transoid (anti) positions relative to

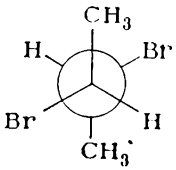
* The φ designations are given here and elsewhere in the book in accordance with the relative position of a pair of substituents which are higher-ranking in atomic number (chlorine in the given case).

one another. This means that the dipole moments of the corresponding bonds will cancel on vectorial addition: the $\varphi^3$-conformation of the *meso*-form must have a zero dipole moment. This will not happen in the preferred $\varphi^1$-conformation of the optically active form. Hence, the optically active form should be naturally expected to have a higher dipole moment than the *meso*-form. This is supported by experiment: *meso*-dichlorostilbene has a dipole moment equal to 1.27 D, while the dipole moment of racemic dichlorostilbene is 2.75 D. The same ratio is observed for hydrobenzoin

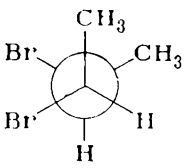


The dipole moment of the *meso*-form of hydrobenzoin equals 2.08 D, while the racemic form has a dipole moment of 2.67 D. If a compound contains, as substituents, groups which are themselves capable of existence in different conformations, the situation may become complicated; such is the case, for example, with the diastereomeric diethyl esters of tartaric acids.

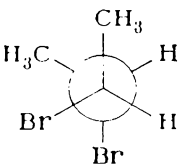
Let us consider in more detail the studies of the conformations of 2,3-dibromobutane (68). *meso*-2,3-Dibromobutane exists predominantly in the transoid ($\varphi^3$) conformation (70 per cent), the remaining 30 per cent being made up of the fractions of two conformations with the skew (gauche) disposition of identical substituents:



$\varphi^3$, 70%

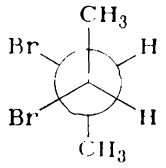


$\varphi^1$, 15%

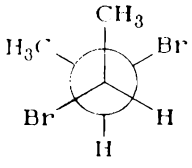


$\varphi^5$, 15%

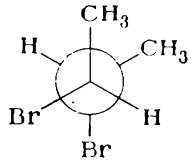
The racemic diastereomer of 2,3-dibromobutane exists predominantly in the $\varphi^1$-conformation, the conformation $\varphi^5$ being the least favourable (about 20 per cent):



$\varphi^1$



$\varphi^3$



$\varphi^5$

The fact that the $\varphi^3$-conformation of the *meso*-form is preferred is understandable: there are only two skew interactions in it against three skew interactions in the other conformations. But the preferableness of the $\varphi^1$-conformation of the optically active form is unexpected: in this case there are three skew interactions, while the $\varphi^5$-conformation has only two such interactions, which, one would think, must contribute to the stability of the latter conformation. Such an approach, however, does not take into account the *nature* of the interactions involved and the excess energy produced by these interactions. For a quantitative approach, use may be made of the data on the conformational energy (12) (see also page 232). For the interactions of interest we have the following data: 6.6 kJ/mole for the Br-Br interaction; 10.7 kJ/mole for the $CH_3$-$CH_3$ interaction; 3.0 kJ/mole for the $CH_3$-Br interaction. Using these values, we can calculate the conformational energies of the conformers involved (Table 4.6).

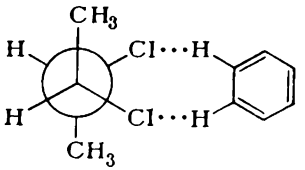
TABLE 4.6. THE ENERGIES OF VARIOUS CONFORMATIONS OF 2,3-DIBROMOBUTANE

| Conformation | Types of non-bonded interactions and their number | | | Total energy, kJ/mole |
|---|---|---|---|---|
| | Br-Br | $CH_3$-$CH_3$ | $CH_3$-Br | |
| *The meso-form:* | | | | |
| Conformer $\varphi^3$ | None | None | 2 | 6.0 |
| Conformer $\varphi^1$ | 1 | 1 | 1 | 20.3 |
| Conformer $\varphi^5$ | 1 | 1 | 1 | 20.3 |
| *The racemic form:* | | | | |
| Conformer $\varphi^1$ | 1 | None | 2 | 12.6 |
| Conformer $\varphi^3$ | None | 1 | 2 | 16.7 |
| Conformer $\varphi^5$ | 1 | 1 | None | 17.3 |

From Table 4.6 it is seen that the greater the conformational energy, the lower is the fraction of the corresponding conformer in the equilibrium.

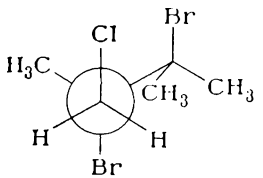
2,3-Dichlorobutane has also been investigated in detail (69). The strong effect of benzene (as a solvent) on the conformational equilibrium has been noted for this compound. It is believed that this is the result of intermolecular association which causes a shift of the conformational

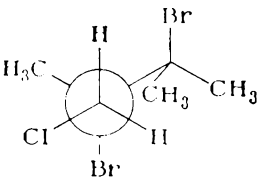
equilibrium to the side of the skew form:




A particularly strong effect is exerted by a solvent on the conformational equilibrium of the *meso*-form of 2,3-dichlorobutane; the population of the transoid conformation decreases with increasing polarity of the solvent (it is 63 per cent in carbon tetrachloride and 33 per cent in acetonitrile).

In studying di- and trihalogen derivatives of 2,3-dimethylbutane one must of necessity take into account the conformations around two carbon-carbon bonds. The main conclusion that has been made in the study of these compounds (70) is that the least favourable are conformations in which there is observed a 1,3-eclipsing of halogen atoms, which is similar to the 1,3-diaxial interaction in cyclohexane. It is for this reason that of the two conformations of 2,3-dibromo-1-chloro-2,3-dimethylbutane the second one is more favourable, in spite of the chlorine and bromine atoms being in the skew position in it:



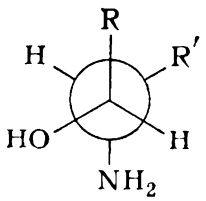




A study of compounds of the type R—CHX—CHX—R (X = various halogen atoms) has shown that the *erythro*-isomer exists predominantly in the transoid conformation, while the preferred conformation of the *threo*-isomer is the skew conformation (71). The conformations of compounds of the type Ar—CHX—CHY—R, where X and Y are halogen atoms, hydroxyl group and amino group in various combinations have also been investigated by means of NMR spectroscopy (72).

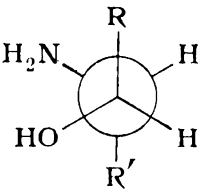
The diastereomeric amino alcohols studied by Drefahl and coworkers (73) belong to the same category of compounds. They serve as examples of compounds, the conformations of which are determined not only by purely steric factors but also by the tendency towards the formation

of an intramolecular hydrogen bond between the two functional groups present. The IR spectra of these amino alcohols point to the presence of such a bond, which is possible in the following conformations (the φ-notation reflects the relative disposition of the OH and $NH_2$ groups):

*threo*-Form

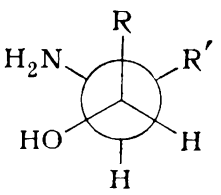



$\varphi^5$

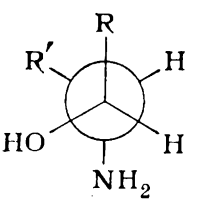



$\varphi^1$

*erythro*-Form



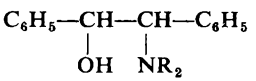

$\varphi^1$




$\varphi^5$

Based on the IR spectra, Drefahl and coworkers have come to the conclusion that the preferred conformation of the *threo*-form is $\varphi^5$ and for the *erythro*-form the two conformations shown are equally probable.

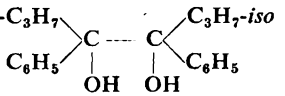
The conformations of related amino alcohols of the structure




have been studied by the proton magnetic resonance method (74); judging by the spin-spin coupling constants, the *threo*-form exists almost entirely (by 90 per cent) as the $\varphi^5$-conformer.

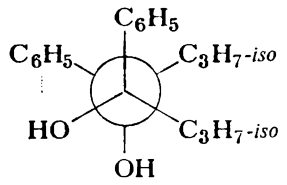
The equation given earlier (see page 251) was used for calculation: $J_{skew}$ is assumed to be equal to 2.6 cps and $J_{trans}$ to 10.3 cps.

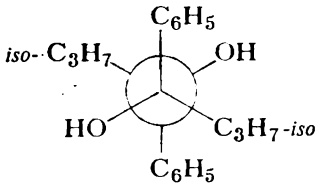
Hydrogen bonds play a definite part in the conformational equilibrium of diastereomeric phenylisopropylpinacols too (75):



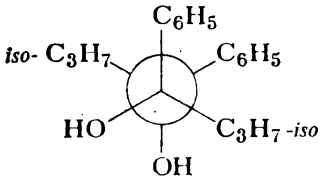
According to the IR and PMR spectral data, each of the diastereomers exists in two conformations ($\varphi^5$ on the right and $\varphi^3$ on the left for the *meso*-form, and the conformation $\varphi^1$ for the racemate).

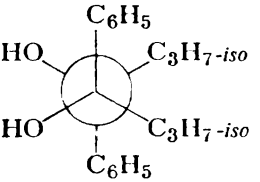
*meso*-Form



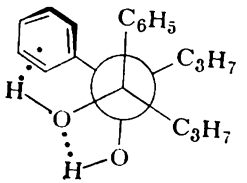




Racemic form

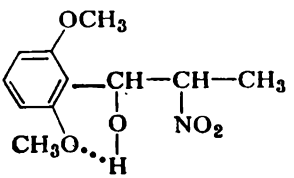


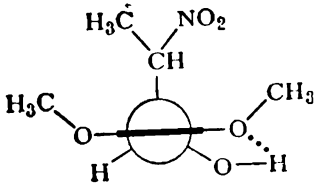

The presence of the $\varphi^3$-conformation in the *meso*-form is detected from the IR spectra where, apart from the band of the bound hydroxyl group (3565 $cm^{-1}$), there is a band of the free hydroxyl group (3610 $cm^{-1}$). It is believed (75) that, in addition to the hydrogen bond between the hydroxyl groups in the $\varphi^5$-conformation of the *meso*-form, there is a hydrogen bond involved in the benzene ring:



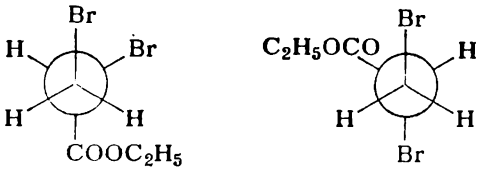

A very peculiar stable hydrogen bond has been detected by means of IR and PMR spectroscopy in the molecule of *threo*-1-(2′,6′-dimethoxyphenyl)-1-hydroxy-2-nitropropane (76):



This hydrogen bond between the OH group of the side chain and the $CH_3O$ group leads to the formation of another conformation around the $C_{arom} - C_{aliph}$ bond marked with a red line in the formula given above (the filled rectangle in the Newman formula shown below denotes the benzene ring):

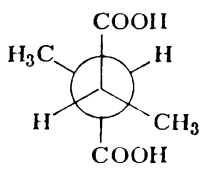



Extensive material has been collected on the conformations of compounds containing the carboxyl function in combination with other substituents—halogens, hydroxyl group. For instance, for the ester of 2,3-dibromopropionic acid (77), the second of the two conformations given below is more stable as evidenced by the PMR data:

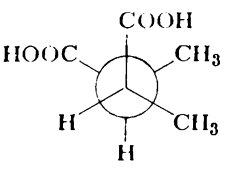



Another example was used to study the effect of a solvent on the conformational equilibrium (78). The investigations were carried out on α,α′-dimethylsuccinic acids:

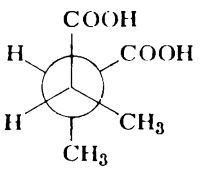
*meso*-Form




XXXa

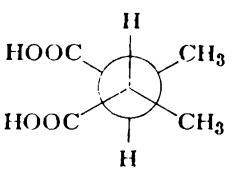



XXXIa

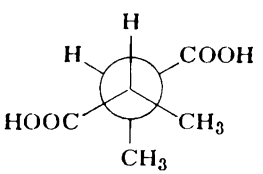



XXXIIa

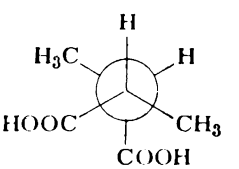
Racemic form




XXXb




XXXIb




XXXIIb

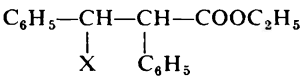
The conformer XXX is the most favourable for both diastereomers. Its fraction (in per cent) in various solvents is as follows:

| | Water | Acetone | Pyridine | Sodium salt in water |
|---|---|---|---|---|
| XXXa | 50 | 65 | 65 | 80 |
| XXXb | 70 | 60 | 55 | 55 |

According to the opinion of the authors of the work under discussion, the following three factors are responsible for this result:

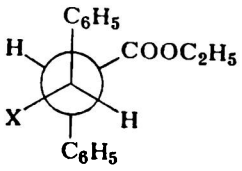
1. The number and nature of skew interactions. In the racemic form as well as in the *meso*-form, this factor contributes to the formation of conformation XXX.
2. The formation of intramolecular hydrogen bonds. These bonds contribute to the formation of conformations XXXIa and XXXIIa in the *meso*-form and of conformations XXXb and XXXIIb in the racemic form.
3. The dielectric constant of the solvent: its increase reduces the repulsion of polar groups, encouraging the creation of conformations XXXIa and XXXIIa for the *meso*-form and of conformations XXXb and XXXIIb for the racemic form.

The *threo*- and *erythro*-forms with their lower symmetry as compared with the *meso*- and racemic forms offer even greater possibilities for the existence of various conformations. Spassov (79), using the PMR method, studied the conformational equilibrium for the *threo*- and *erythro*-forms of compounds of the type

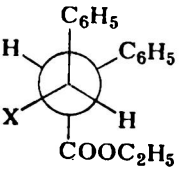


where X = OH, $NH_2$, $NHC_6H_5$, $NHCONH_2$.

A conformer with the transoid arrangement of hydrogen atoms is preferable for both diastereomers:



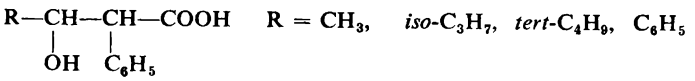

*erythro*-



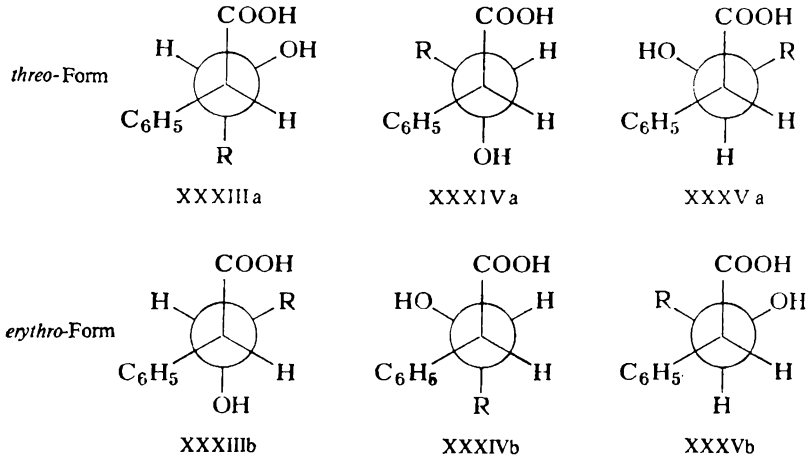

*threo*-

Why these conformations are preferred can be simply explained by means of an ordinary conformational treatment: these conformations have each two skew interactions, the others (not shown here) having each three such interactions.

A study of the conformations of the *threo*- and *erythro*-forms of β-hydroxy acids (80) of the type



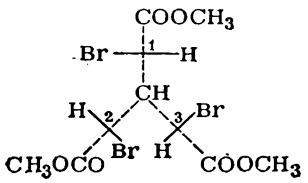

by means of a number of methods (IR and PMR spectroscopy, cryoscopic determinations of the apparent molecular mass) has shown that the *threo*-form exists in the preferred conformation XXXIIIa, while in the *erythro*-form all the three conformations are nearly equivalent:

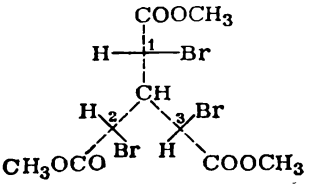



The predominance of conformation XXXIIIa with a strong intramolecular hydrogen bond in the *threo*-form results in this form being less associated and having a lower apparent molecular mass. In solvents capable of forming hydrogen bonds, the conformational equilibrium of the *erythro*-form is displaced to the side of conformation XXXIIIb since the intramolecular hydrogen bonds, which are present in forms XXXIVb and XXXVb and which stabilize them, are replaced by intermolecular hydrogen bonds in the presence of a solvent.

Of the other investigations concerned with diastereomeric carboxylic acids, mention should be made of the work of Velichko *et al.* (81), in

which the configurations of the *meso*- and racemic forms of 2,4-dibromoglutaric acid are finalized, and also of the work carried out by Mock (82) and devoted to the study of the spatial forms of a compound in which three α-bromoacetic acid residues are linked to the central carbon atom. This compound was resolved into two diastereomeric forms by crystallization from methylcyclohexane:




The first of these formulas was termed the bisracemic formula since a combination of any two of its asymmetric centres corresponds to one of the optical antipodes of the racemic diastereomers with two asymmetric centres; the second form was termed the *meso*-racemic form since a combination of the asymmetric centre 1 with either of the other two centres corresponds to the *meso*-form and a combination of centres 2 and 3 corresponds to the racemic form.

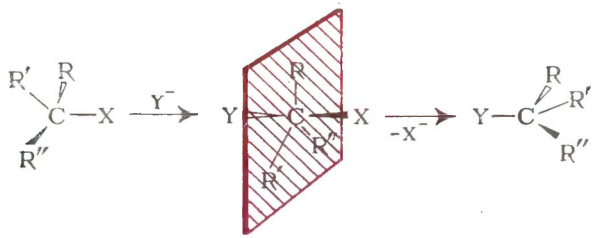
## 4.8. STEREOCHEMISTRY OF REACTIONS OF ACYCLIC COMPOUNDS

### 4.8.1. NUCLEOPHILIC SUBSTITUTION REACTIONS

It has already been pointed out in Chapter 1 that the stereochemical result of substitution reactions at the asymmetric carbon atom is determined by the rules worked out by Ingold: substitution by the $S_N2$ mechanism is accompanied by inversion of configuration, whereas substitution by the $S_N1$ mechanism usually involves racemization or partial inversion of configuration, and if the molecule contains "fixing groups", retention of configuration takes place too. The rules developed by Ingold may be interpreted in the following clear-cut manner.

Reactions taking place by the $S_N2$ mechanism proceed via a transition state in which the entering group interacts with the asymmetric centre at the moment when the bond between the leaving group and this centre has not yet been completely broken. The most favourable model of such a transition state is the arrangement of the entering and leaving

groups on a single straight line from both sides of the asymmetric centre. The substitution in this case leads to inversion of configuration:



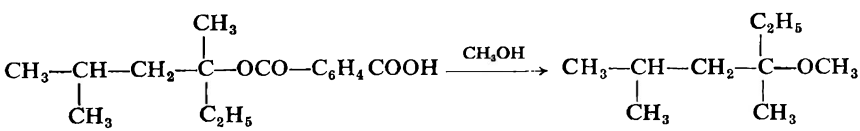
The most spectacular proof of the correctness of the above conceptions of the steric directedness of reactions proceeding by the $S_N2$ mechanism has been obtained by a study of the racemization of optically active halogen derivatives under the action of salts containing a radioactive halogen atom:

$$R{-}X + Na\overset{*}{X} \longrightarrow R{-}\overset{*}{X} + NaX$$

A comparison of the rate of racemization with the data of radiochemical measurements has shown that each individual act of halogen exchange is accompanied by inversion of configuration.

Special studies have demonstrated that the stereochemical result of $S_N2$ reactions is the same for nucleophilic substitution processes at the primary and also at the secondary and tertiary carbon atoms. The investigation into the stereochemistry of substitution reactions at the primary carbon atom became possible only after optically active compounds with a "hydrogen-deuterium asymmetry" has been obtained. As an example may be cited the use of 1-deuteroethanol with a view to proving inversion of configuration on alkaline hydrolysis of its *p*-toluene sulphonate.

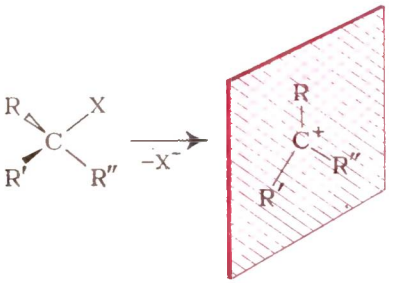
An example of a $S_N2$ reaction proceeding with inversion of configuration at a tertiary asymmetric centre is the methanolysis of the acid phthalate of 2,4-dimethyl-4-hexanol:



An analogous result has been obtained by other authors too (83).

The outcome of a unimolecular nucleophilic substitution reaction may vary in the stereochemical sense. Whether optical activity is retained (with or without inversion of configuration) or racemization takes place

depends, in the long run, on the lifetime of the carbonium ion formed at the first stage of the $S_N1$ reaction. In principle, carbonium ions have a planar structure and when they are formed, asymmetry is lost:




Thus, at the second stage of the reaction the nucleophilic reagent may attack from both sides of the plane with equal probability, i.e., the most natural result of the reaction proceeding by the $S_N1$ mechanism should have been racemization. In fact, however, in the majority of cases there is observed inversion of configuration in addition to racemization. This is accounted for by the fact that the leaving anion $X^-$ hinders the approach to the planar carbonium ion and the nucleophilic reagent attacks from the opposite side, this resembling the course of a substitution reaction taking place by the $S_N2$ mechanism.

The shorter the lifetime of the carbonium ion and the sooner it enters into reaction with the nucleophile after it is formed, the greater the extent of shielding by the anion $X^-$ which has not yet moved to a large distance; hence, the higher is the percentage of inversion. Conversely, the longer the lifetime of the carbonium ion, the greater is the probability of the nucleophile approaching from both sides and the greater is the probability of racemization.

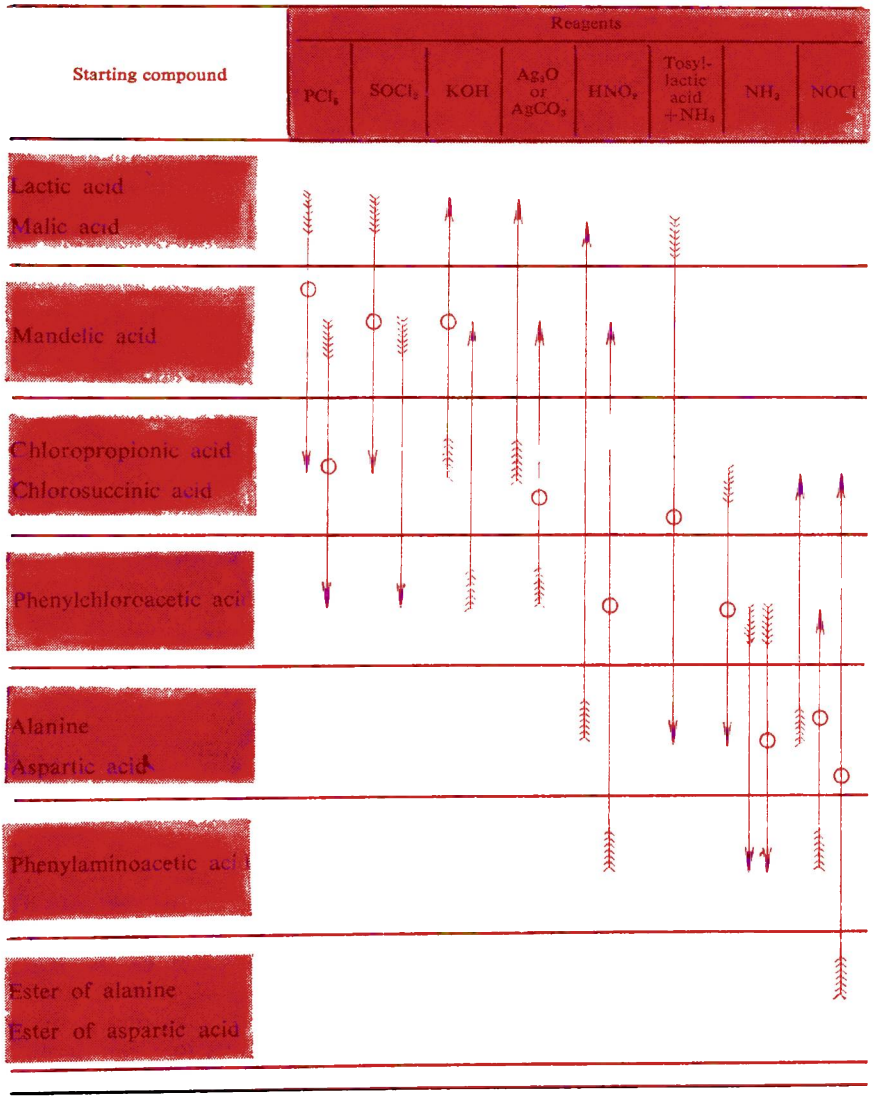
The lifetime of the carbonium ion depends, in its turn, on a number of factors: the structure of the ion itself, the nature of the reagent (its reactivity), the concentration of the reagent, and the nature of the solvent.

Retention of configuration under the influence of "fixing groups" is accounted for by the interaction of the free electron pairs present with the carbonium ion centre. Such an interaction takes place from the rear side, and the nucleophilic reagent has an opportunity to attack the carbonium ion only after the anion $X^-$ has moved sufficiently far away and only from the front and not from the rear.

For a practical orientation in regard to the result of nucleophilic substitution reactions at the asymmetric centre, a table is given here, which is taken from an article by Freudenberg (84) and which indicates the stereochemical results of a number of reactions of this type (see Table 4.7). The arrows with circles indicate the direction of reactions proceeding

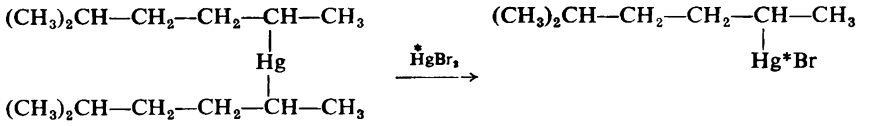
with a Walden inversion, and the arrows without circles signify reactions involving retention of configuration. The generalized topological approach to substitution reactions occurring at the asymmetric centre has been worked out by Garwood and Cram (85).

TABLE 4.7. THE STEREOCHEMICAL RESULT OF NUCLEOPHILIC SUBSTITUTION REACTIONS AT THE ASYMMETRIC CENTRE

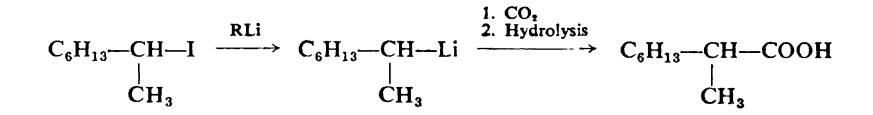


### 4.8.2. ELECTROPHILIC SUBSTITUTION REACTIONS

Extensive studies of electrophilic substitution reactions taking place at a saturated carbon atom have been accomplished by Reutov and coworkers, who used organometallic compounds (86). In reactions proceeding by the $S_E2$ mechanism there is observed retention of configuration. It has been demonstrated in the most spectacular way for an isotope exchange reaction involving optically active 2-methylhexyl-5-mercuribromide.



Retention of configuration in $S_E2$ substitution reactions at the saturated carbon atom has also been confirmed in the works of Winstein and Ingold. The problem of retention of optical activity in electrophilic substitution reactions occurring by the $S_E1$ mechanism is connected with the problem of stability of the configurations of carbanions which must serve as intermediate particles in such reactions. The usual result of $S_E1$ reactions is the occurrence of racemization since carbanions become planar and lose asymmetry. It has however been shown that if an exchange reaction between optically active 2-iodooctane and 2-butyllithium with subsequent carbonization is conducted at —70°C, it is possible to isolate 2-methyloctanoic acid with retention of configuration by 80 per cent:



In other reactions, inversion of configuration too has been observed. The stereochemistry of reactions involving carbanions is treated in more detail by Cram (87).

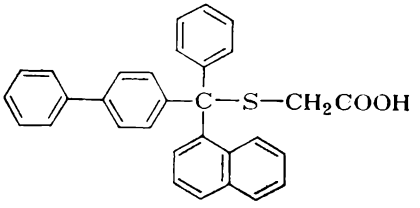
### 4.8.3. REACTIONS INVOLVING FREE RADICALS

Of decisive importance for the stereochemical result of free-radical reactions which involve the change of the asymmetric centre is the question of whether optical activity is retained in free radicals. Most of the works point to the necessity of giving the negative answer to this question. Thus, optically active acid XXXVI with an asymmetric atom of the triarylmethane type undergoes racemization on interaction with

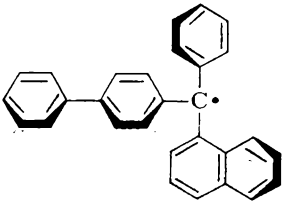
triphenylmethyl radicals; it is believed that this occurs because of the loss of asymmetry by the transiently formed radicals XXXVII.

The fact that attempts to obtain radicals XXXVII in an optically active form by chromatography on optically active sorbents have failed is also considered to be an indication of the planar structure of triarylmethyl radicals.

Mention should however be made here of the asymmetric synthesis developed by Karagounis and Drykos (see page 153), in which the formation of an optically active substance was revealed in the course of the bromination of radical XXXVII by illumination with circularly polarized light. This result is an evidence in favour of asymmetry and the radical itself. True, at present, an asymmetry of the spiral rather than tetrahedral type is considered to be more probable (cf. page 511).

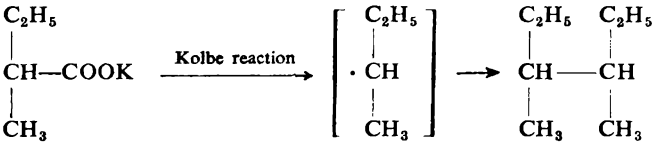



XXXVI

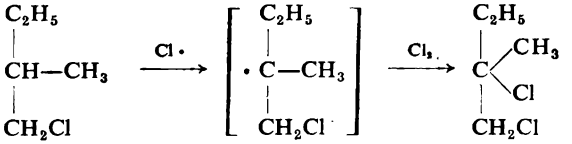



XXXVII

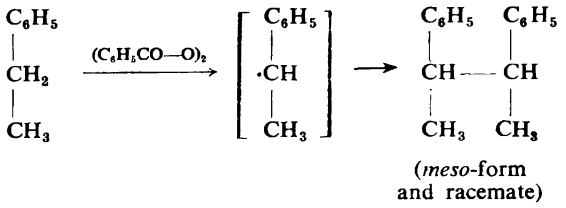
Of more general importance is the problem of retention or loss of the tetrahedral configuration by the intermediate radical particles formed during the course of homolytic reactions. Here again the majority of works indicate the loss of optical activity by radicals. Thus, in the electrolysis of an optically active salt of 2-methylbutyric acid, which results in the formation of 3,4-dimethylhexane (the Kolbe reaction), the reaction product is found to be inactive, which means that the radicals formed during the course of this transformation are also inactive:




The racemization of the transiently formed free radical is also considered to be responsible for the loss of optical activity in the process of photochemical chlorination of 1-chloro-2-methylbutane:

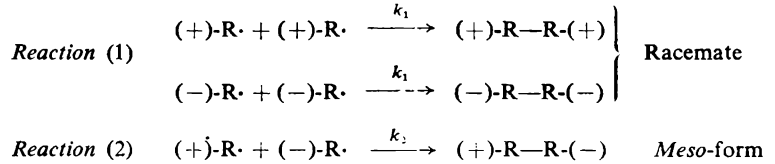


The retention or loss of configuration by the radical centre can be studied not only on optically active substances; for this purpose, use may also be made of reactions involving diastereomers. For example, α-phenylethyl radicals formed by the action of benzoyl peroxide on ethylbenzene undergo dimerization with the formation of the racemic and *meso*-forms of 2,3-diphenylbutane:



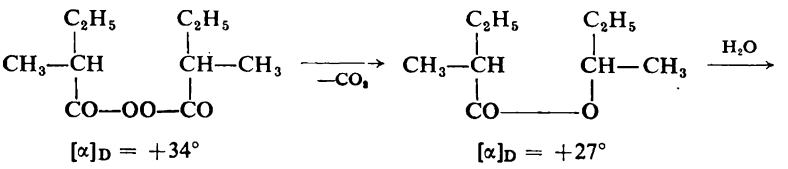

(*meso*-form and racemate)

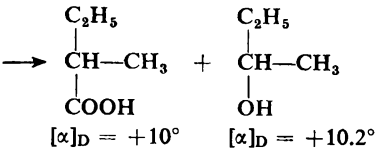
The fact that this gives *equal* amounts of the *meso*-form and racemate is an indication of the absence of stereospecificity in the course of dimerization. Incidentally, with the participation of asymmetric radicals there should be expected differences in the rates of reactions (1) and (2) and the formation of *different* quantities of the *meso*-form and racemate ($k_1 \neq k_2$):




The same result has been obtained (88) in the study of the dimerization of α-phenylethyl radicals obtained by the action of divalent chromium on α-phenylethyl chloride and by other methods. The predominance of the *meso*-form in the reaction products reported in the literature is refuted in the work under consideration.

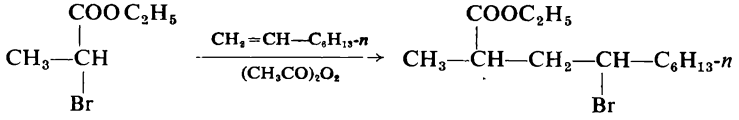
There are works which may be interpreted as evidence of the retention of the tetrahedral configuration of radicals. Thus, in the pyrolysis of optically active isovaleryl peroxide, which leads to the formation of *sec*-butyl 2-methylbutyrate, the reaction proceeds with retention of the configuration of both asymmetric centres:






For the interpretation of this unusual retention of optical activity it has been suggested that this reaction be regarded as a non-radical reaction, which however, contradicts the usual approach to the mechanism of the decomposition of peroxides.

Retention of optical activity has also been observed during the course of the radical reaction between ethyl (—)-2-bromopropionate and 1-octene:




Despite these results, it is generally believed at present that an unpaired electron is incapable of fixing the configuration of the radical. Therefore, all reactions that proceed through the stage of formation of free radicals involve racemization, with rare exceptions.

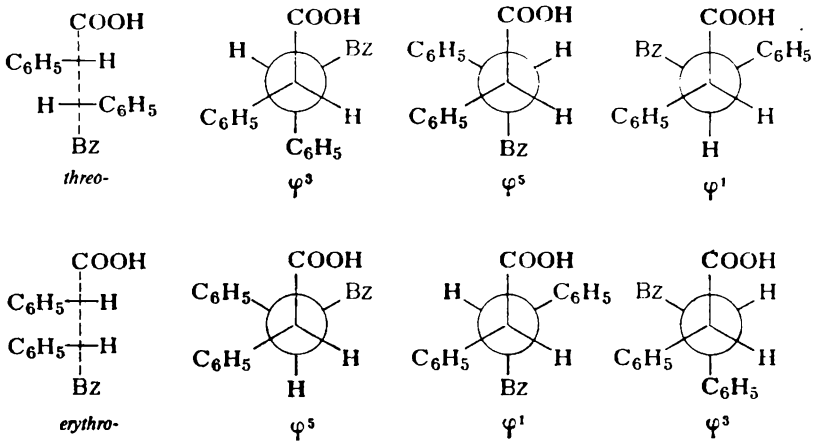
The stereochemistry of free-radical reactions is discussed in more detail by Williams (89).

### 4.8.4. DIFFERENCES IN THE REACTIVITY OF DIASTEREOMERS

Numerous observations were made as early as last century regarding differences in the reactivity of diastereomers. At that time it seemed quite inexplicable why substances that had the same chemical constitution showed differences in the rates and even in the directions of many reactions. The cause of these differences became understandable only on the basis of conformational conceptions. The corresponding reactions of diastereomers are, in the majority of cases, elimination reactions involving the formation of a double bond, which is why they will be treated in more detail in the chapter devoted to the stereochemistry of compounds containing multiple bonds. Here we shall cite only one example concerning the reaction of cyclization of 2,3,4-triphenylbutyric acid (90).

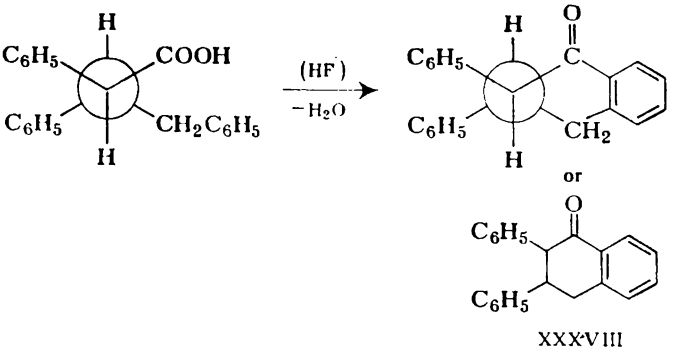
Possessing two asymmetric centres, 2,3,4-triphenylbutyric acid exists as two diastereomers—the *threo*- and *erythro*-forms, each of which is a racemate formed by a pair of optical antipodes (enantiomers). Let us write down the configurations and conformations for one antipode of each pair; for the other antipode the disposition of the groups in

Newman formulas will be a mirror-image, the relations between them do not change, and all our reasoning remains valid for the other pair too (the φ designations given below reflect the relative disposition of phenyl and carboxyl groups which are groups of highest priority on counting the atomic numbers).



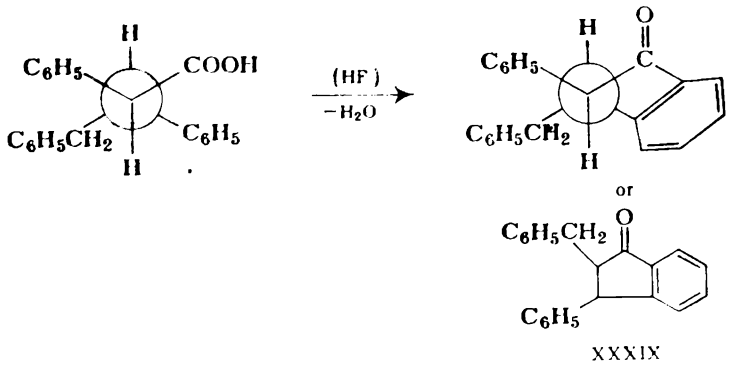

Bz= $CH_2C_6H_5$

The preferred conformation of the *threo*-form is $\varphi^3$, and that of the *erythro*-form is $\varphi^1$ because the bulky substituents are arranged in pairs (two skew interactions) in these conformations and successively, one after another (three skew interactions), in the other conformations. In the $\varphi^3$-conformation of the *threo*-form, the carboxyl group is close to the phenyl group at $C_4$, and cyclization occurs with the participation of this group and formation of a new six-membered ring:




XXXVIII

In the stable $\varphi^1$-conformation of the *erythro*-form, the carboxyl group is close to the phenyl group at $C_3$ and, as a result of the cyclization, there is formed a new five-membered ring:




XXXIX

According to the predictions made on the basis of conformational analysis, from the *threo*-isomer there is really predominantly formed a compound with a six-membered ring (the XXXVIII: XXXIX ratio is 2 : 1), and from the *erythro*-isomer there is predominantly obtained a compound with the five-membered ring (the XXXVIII : XXXIX ratio is 1 : 3).

Not only the reactivities of diastereomers are different, but also the probabilities of their formation. Reactions of this kind include, for example, transformations in the course of which a second asymmetric atom is formed from a carbonyl group in a compound having a chiral centre. The Prelog and Cram rules considered in Chapter 2 (see pages 122 and 132) apply to reactions of this type.

## 4.9. OPTICAL ACTIVITY

### 4.9.1. BASIC CONCEPTIONS

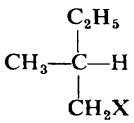
Optically active substances can be found in all classes of organic compounds—aliphatic, saturated and unsaturated, alicyclic, aromatic, and heterocyclic compounds. The question of optical activity will therefore be treated in all the chapters of this book, and the concept of the various types of optically active compounds will be gradually broadened. The basic conceptions in the field of optical activity of organic compounds have been developed on the basis of the simplest aliphatic compounds.

The tetrahedral model of the carbon atom put forward by J.H. van't Hoff was at first a hypothesis that offered a satisfactory explanation for

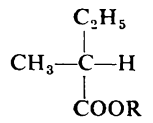
the known facts. This hypothesis could be developed further and confirmed at that time only by way of experimental verification of the correctness of the conclusions that followed from the tetrahedral model. For this purpose, a number of investigations were carried out in the eighties and nineties of last century and later on, some of which look at present like a proof that two and two makes four. But at that time these works were of fundamental importance.

It was necessary to clarify the question whether the presence of an asymmetric carbon atom was invariably a must for the appearance of optical activity (compounds with molecular asymmetry are left out for the present). The literature of that time reported examples of substances which were believed to display optical activity *with no* asymmetric atom present. Among the compounds cited was styrene, $C_6H_5—CH=CH_2$. Van't Hoff carried out a special experiment in order to prove that the plane of polarization was actually rotated not by styrene itself but by the impurity contained in it. Having treated 10 kg of styrene of natural origin (from the resin styrax), van't Hoff succeeded in isolating 3 g of this impurity, a compound belonging to the class of bicyclic terpenes.

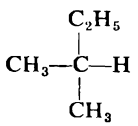
A proof that the presence of an asymmetric carbon atom is really responsible for the manifestation of optical activity has been provided by many experiments showing that optical activity is lost as soon as the asymmetric atom disappears. Thus, numerous derivatives of optically active amyl alcohol, compounds of the XL and XLI types, retain optical activity unless they lose their asymmetric carbon atom. As soon as these compounds are converted into compounds XLII or XLIII, which contain no asymmetric carbon atom, their optical activity is lost.



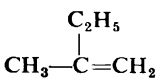
XL



XLI



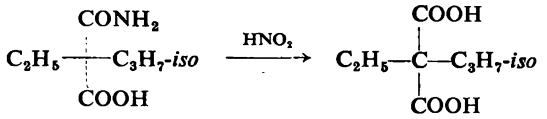
XLII



XLIII

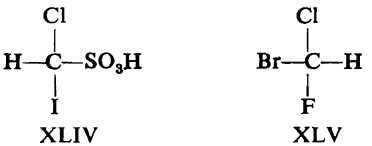
Tartaric acid retains its optical activity after being transformed into the various derivatives at carboxyl or hydroxyl groups, but it becomes optically inactive when converted into succinic acid which has no centre of asymmetry. Another work of the same kind was accomplished in 1913 by Emil Fischer who proved that the optically active monamide

of a substituted malonic acid loses its activity when it is converted into the free acid:



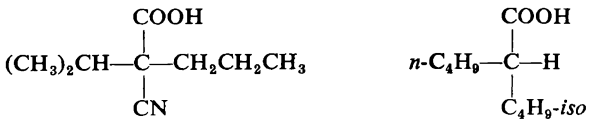
This proof was more rigorous than the previous ones since the reaction was conducted under considerably milder conditions, which reduced the possibility of racemization to a minimum.

Logically, it was also important to provide an answer to the question whether a substance containing *only one* carbon atom would be optically active provided that it was asymmetric. A substance of this kind was first synthesized in 1914; it was optically active chloroiodomethanesulphonic acid XLIV. Another analogous model, (+)-bromochlorofluoromethane XLV, has been obtained only recently (91).



XLIV XLV

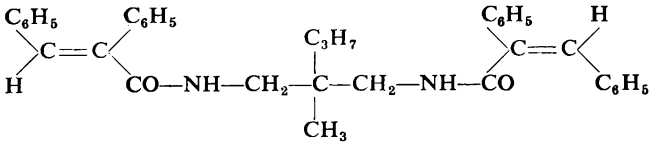
An answer was also required to the question: To what extent must the substituents be different for a compound to acquire asymmetry and, hence, optical activity? The answer to this question was given by Emil Fischer who showed that for a considerable value of rotation to be obtained it is sufficient that the substituents at the asymmetric centre be isomeric at least; examples are compounds XLVI and XLVII:



XLVI XLVII

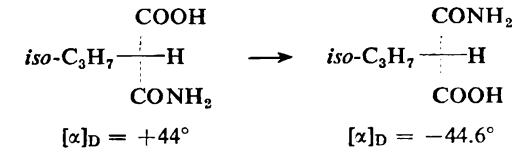
$[\alpha]_D = +11.4°$ $[\alpha]_D = +5.73°$

In the fifties of this century Rimschneider showed that the *cis-trans* isomerism of two substituents situated at the asymmetric atom is sufficient for a compound to become optically active:



$[\alpha]_D$ is about 0.7°

One of the fundamental consequences of the tetrahedral model is the transformation of a compound into its antipode (enantiomer) when the two substituents at the asymmetric centre exchange their places. Emil Fischer carried out such an exchange reaction without disturbing the asymmetric centre, by making the carboxyl and amide groups to exchange their places in the monamide of isopropylmalonic acid. The experimental realization of the inversion required a number of intermediate conversions, the final result of which was as follows:




Note that the configurations are written arbitrarily in our scheme: they were not determined experimentally. The entire conversion consisted of five consecutive reactions.

The positive answer has been obtained to the question whether the *isotopic* difference between the substituents situated at the asymmetric centre is sufficient for the appearance of optical activity (92). As a result, a number of compounds with a "deuterium-hydrogen asymmetry" have been produced and used in stereochemical studies, for example, 1-deuteroethanol, $CH_3$—CHD—OH, and deuterated benzylamine, $C_6H_5$—CHD—$NH_2$. As has already been mentioned (see page 267), these compounds play an important part in stereochemical investigations.

### 4.9.2. CHUGAEV'S RULE

At the turn of the 19th century Chugaev carried out a series of works devoted to the investigation of optically active compounds, which made a substantial contribution to science. Chugaev put forward an idea that for the optical activities of different compounds to be compared, use should be made not of specific but of molecular rotations as constants directly associated with the equal molar fractions of the compound. The analysis of the values of molecular rotation of homologues allowed Chugaev to formulate two important rules (93).

1. The principle of constancy of molecular rotation within the homologous series. Using experimental data obtained by him and other investigators, Chugaev showed that the value $[M]$ is constant in homologous series if the first members are omitted. As an example may serve the following comparison of the values of rotation of the esters of menthol and amyl alcohol with the homologous fatty acids:

| Acid | $[M]_D^{20}$ of ester of (−)-menthol | $[M]_D^{20}$ of ester of (−)-amyl alcohol |
|---|---|---|
| Formic acid | −146.3° | −2.33° |
| Acetic acid | −157.3° | −3.29° |
| Propionic acid | −160.2° | −3.99° |
| Butyric acid | −156.9° | −4.25° |
| Valeric acid | −157.3° | −4.33° |
| Caprylic acid | −155.8° | −4.49° |
| Palmitic acid | — | −4.17° |
| Stearic acid | — | −4.49° |

The same law is obeyed by the esters of optically active valeric (butane-2-carboxylic) acid, the esters of glyceric acid with the homologous alcohols and other series of homologues. Analogous data were obtained later on optically active ketones of the structure

$$C_6H_5—\underset{\displaystyle R}{\underset{|}{CH}}—CO—R'$$

which have the following values of $[M]_D$ in cyclohexane solutions:

| R | R′ | $[M]_D^{20}$ | R | R′ | $[M]_D^{20}$ |
|---|---|---|---|---|---|
| $CH_3$ | $CH_3$ | 1280° | $C_2H_5$ | $CH_3$ | 1070° |
| $CH_3$ | $C_2H_5$ | 1120° | $C_2H_5$ | $C_2H_5$ | 1050° |
| $CH_3$ | $C_3H_7$ | 1190° | $C_2H_5$ | $C_3H_7$ | 1050° |
| $CH_3$ | $C_4H_9$ | 1060° | | | |

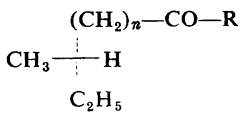
2. The principle of disposition of the substituent being introduced. The closer the substituent is to the asymmetric centre, the more pronounced is its effect on optical activity; as the substituent gradually moves away from the asymmetric centre its effect is gradually weakened and, finally, becomes negligible. To illustrate, Chugaev cited the values of rotation, $[M]_D$, for esters of menthol and amyl alcohol with phenylal-

kanoic acids. At a later time, analogous data were obtained by Nerdel for a series of optically active carbonyl compounds:

| | $CH_3$ | R ... $COCH_2CH_3$ | $CH_2COCH_3$ | $CH_2CH_2CHO$ | $C_3H_7$ |
|---|---|---|---|---|---|
| R—CH< | $C_2H_5$ | $[M]_D$ ... +36.6° | +11·0° | +12.0° | +9.8° |

Thus, as the carbonyl group moves away from the asymmetric centre its effect on the rotation is gradually weakened and then becomes insignificant with two methylene groups separating it from the asymmetric centre.

More thorough studies with the use of the spectropolarimetric method have shown that as the chromophore moves away from the asymmetric centre not only the rotation is simply decreased but the Cotton effect characteristic of the given chromophore gradually disappears and when the chromophore shifts from the α- to the β-position the sign of the Cotton effect is reversed. One example is the study carried out by Djerassi (94) on the same carbonyl compounds that had been investigated by Nerdel (Fig. 4.5).



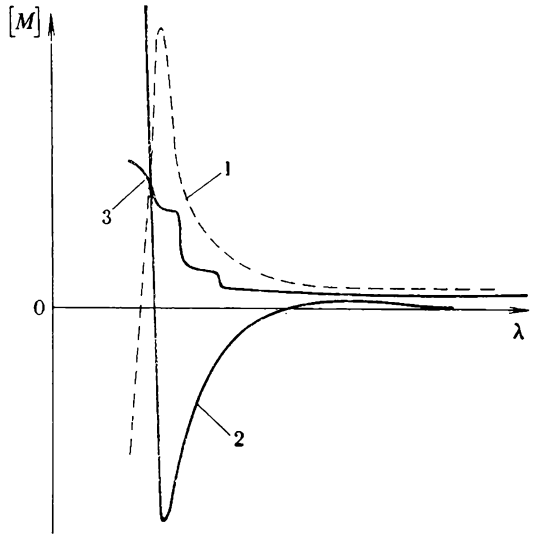
XLVIII

Similar observations were also made for compounds with other chromophores (95). The reversal of the sign of the Cotton effect upon shift from the α- to the β-position was named the "vicinity rule" or the "β-effect".

### 4.9.3. PHYSICAL FOUNDATIONS OF OPTICAL ROTATION

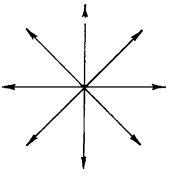
From the standpoint of classical wave theory of light, the light wave is considered to be the transverse vibrations of electrical and magnetic vectors, the latter being perpendicular to the former. If the direction of the transverse vibration of the vector is fixed in a certain single plane, the wave becomes plane-polarized (the term "linearly polarized" is also used). The plane mentioned is called the plane of polarization of light. The polarized light beam has the property of **anisotropy**—its properties are different in different directions perpendicular to the line of its propagation. There are no such differences in natural (unpolarized) light since the vector changes direction randomly. The direction of vibrations

Figure 4.5.




*The optical rotatory dispersion curves of carbonyl compounds of the type XLVIII:* **1** *— with* $n = 0$ *;* **2** *— with* $n = 1$ *;* **3** *— with* $n = 2$.

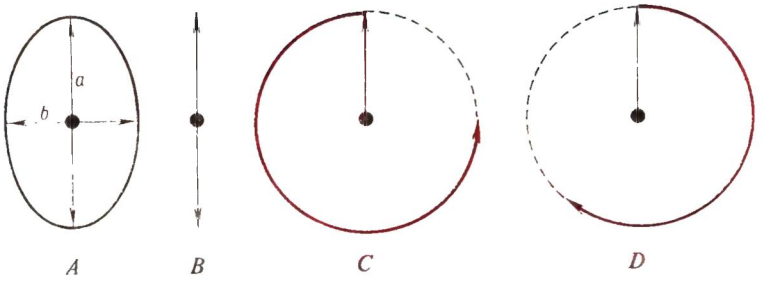
in the cross section of a transverse wave of ordinary light (which propagates perpendicularly to the plane of the drawing) may be schematically shown as follows:



Plane-polarized light with a definite (vertical in the drawing) plane of vector vibrations can be pictured in the same way (see Fig. 4.6*B*).

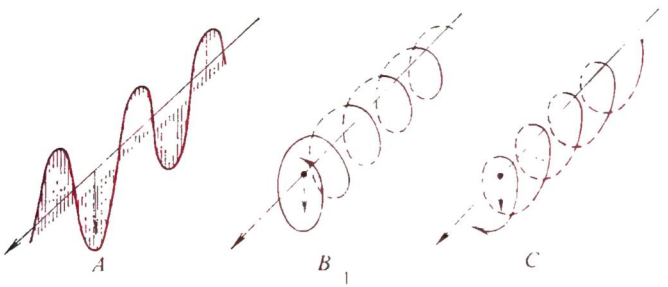
Apart from the linear type, other types of polarization of the transverse wave are also possible. Thus, if the vector oscillates in one plane perpendicular to the direction of propagation of the light beam but the end of the vector describes an ellipse, then such light is elliptically polarized (Fig. 4.6*A*). If the principal axes of the ellipse are equal, the end of the vector will describe a circle; this is circularly polarized light (Fig. 4.6*C* and *D*). Linearly polarized light may be considered to be a special case

Figure 4.6.




*Types of polarization of the transverse wave:*
*A — elliptically polarized light ; B — linearly polarized light ; C — left-circularly polarized light ; D — right-circularly polarized light.*

Figure 4.7.

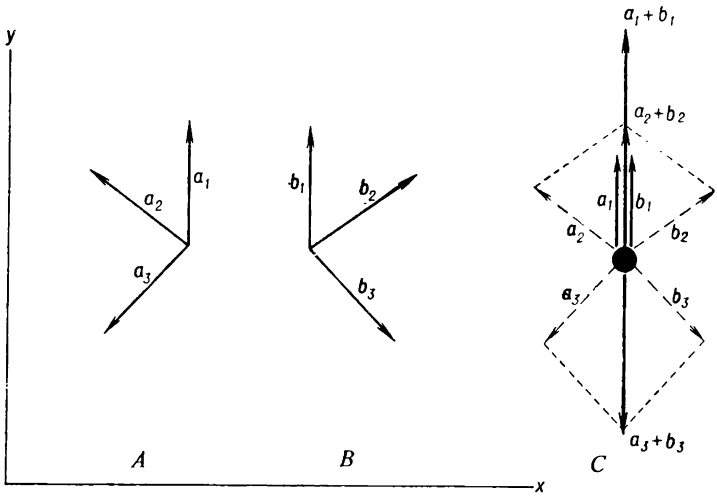



*Linearly polarized wave (A) and circularly polarized waves (B—left, C—right)*

of elliptical polarization at $b = 0$ (Fig. 4.6*A* and *B*). For more clarity, linearly and circularly polarized light waves may be shown in a perspective projection (Fig. 4.7).

Recall also that the linearly polarized beam can be produced by addition of the left- and right-circularly polarized beams. Suppose (see Fig. 4.8) that at times $\tau_1$, $\tau_2$, and $\tau_3$ the electric vectors of the right-circularly polarized beam have the directions $b_1$, $b_2$, $b_3$; the directions for the left-circularly polarized beam will accordingly be $a_1$, $a_2$, and $a_3$. When the vectors are geometrically added up, the $x$-component will be eliminated and a straight line, i.e., a linearly polarized beam, will obtain (see Fig. 4.6*B*).

Figure 4.8.




*Addition of left- and right-circularly polarized beams:*

*$a_1$, $a_2$, $a_3$ — directions of vibrations of the left-circularly polarized beam at times $\tau_1$, $\tau_2$, $\tau_3$ (A); $b_1$, $b_2$, $b_3$ — directions of vibrations of the right-circularly polarized beam at the same time moments (B); the result of the addition (A + B) is the linearly polarized beam (C) (see Fig. 4.6).*

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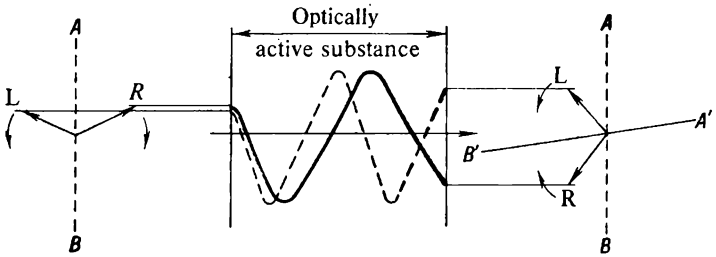
Figure 4.9.




*Rotation of the plane of polarization of light when passed through an optically active substance:*

*AB — the plane of polarization when the light ray enters the substance; A'B'—the plane of polarization when the light ray issues from the substance.*

---

We know that the velocity of propagation of light in a substance, $v$, is related to the refractive index $n$ by the following equation ($c$ is the velocity of light in vacuum):

$$v = c/n \qquad (1)$$

---

As early as 1823 Fresnel established experimentally that the refractive indices of optically active quartz are different for the left and right circularly polarized beams. This means, with account of relation (1), that the two circularly polarized beams propagate at different velocities in an optically active medium: $v_L \neq v_R$. Thus, when linearly polarized light passes through an optically active substance, one of its components (left- or right-circularly polarized ray) will propagate faster than the other. As a result of this, at each given point on the path there will be a phase shift between the two components, which will be the greater the larger is the difference between the velocities $v_L$ and $v_R$ (and, accordingly, between the refractive indices $n_L$ and $n_R$) and the longer the path covered by the beam in the optically active medium. Geometrical addition of the left- and right-circularly polarized components leaving the optically active medium gives a linearly polarized ray, the plane of oscillations of which will be turned at a certain angle $\alpha = \varphi/2$, where $\varphi$ is the angular phase shift of the left- and right-circularly polarized light leaving the optically active medium. Graphically, this can be pictured in the manner shown in Fig. 4.9.

The quantity $\alpha$ is related to the refractive indices $n_L$ and $n_R$ as follows:

$$\alpha = \frac{\pi l}{\lambda_0}(n_L - n_R) \qquad (2)$$

where $l$ is the layer thickness of the optically active substance and $\lambda_0$ is the wavelength in vacuum. From this relation, with account taken of the relationship between the refractive index and the light velocity, in accordance with Eq. (1), it follows that the rotation is positive if the right-circularly polarized beam propagates faster than the left-circularly polarized component, i.e., $n_R < n_L$.

It is instructive to calculate the difference between the refractive indices of the two circularly polarized beams for ordinary optically active substances. Assume that $[\alpha]$ at 500 nm is equal to 100°, i.e., $\alpha = 10°$ per 1 cm, which is $10 \times 2\pi/360$ in radians. Considering that $500\,\text{nm} = 5 \times 10^{-5}$ cm and substituting the appropriate values into formula (2), we obtain:

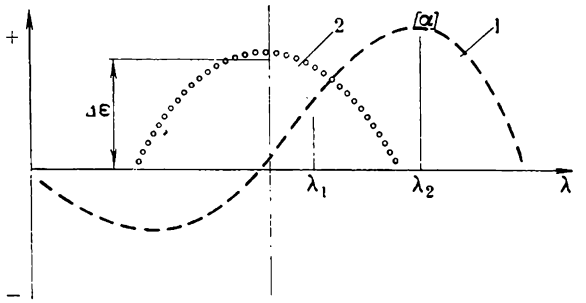
$$\alpha = \frac{10 \times 2\pi}{360} = \frac{\pi}{5 \times 10^{-5}}(n_L - n_R)$$

Hence

$$n_L - n_R = 10 \times \frac{2 \times 5 \times 10^{-5}}{360} = 2.8 \times 10^{-6}$$

Thus, even negligible differences in refractive index between the left- and right-circularly polarized beams, which lie far beyond the accuracy

Figure 4.10.




*The optical rotatory dispersion curve (curve 1) and the circular dichroism curve ($\varepsilon_L - \varepsilon_R$ curve 2).*

limits of ordinary refractometric measurements, are sufficient for large optical rotation to arise. On this basis, the study of optical activity is figuratively termed "intramolecular interferometry", a comparison being thus made with the most sensitive of the other optical methods.

The important concepts in considering optical activity are those of the Cotton effect and circular dichroism (see also page 286).

The **Cotton effect,** which has already been repeatedly mentioned in the text, manifests itself externally in a change of the smooth course of optical rotatory dispersion curves (ORD curves which are plots of optical rotation against wavelength) and in a simultaneous transformation of circularly polarized light into elliptically polarized light at a given wavelength. The absorption bands near which the Cotton effect is observed are called optically active. Within the region of these bands the absorption coefficients for left- and right-circularly polarized light are different; this effect is known as circular dichroism.

The physical picture observed near optically active absorption bands is shown in Fig. 4.10. The Cotton effect shows up as a characteristically shaped ORD curve which is defined (see Fig. 1.20 on page 46) by the **amplitude** (the difference in the magnitude of rotation in the peak and trough, i.e., the vertical distance between the peak and trough), the **width** (the difference between the wavelengths at which the peak and trough are situated, i.e., the horizontal distance) and the spectral position of the peak and trough (or the halfway point between them). On circular dichroism curves (i.e., curves showing the dependence of the difference $\varepsilon_L - \varepsilon_R$ on the wavelength) the Cotton effect manifests itself as a band of intensity $\Delta\varepsilon$, width $d$ and the position of the maximum at wavelength $\lambda_0$.

The relation between the ORD curve and the sign of circular dichroism is expressed by the Nathanson rule which states: if there is an absorption band in which the left-circularly polarized component is absorbed more strongly than the right-circularly polarized component ($\varepsilon_L > \varepsilon_R$), then the rotation observed in the long-wavelength region of this band is more right-handed than in the short-wavelength region:

$$[\alpha]_{\lambda+x} > [\alpha]_{\lambda}$$

The curves in Fig. 4.10 exactly correspond to this case; here $\varepsilon_L - \varepsilon_R > 0$ and $[\alpha]^2_\lambda - [\alpha]^1_\lambda > 0$.

Because of the differences in the absorption coefficients for right- and left-circularly polarized light in the region of the Cotton effect the linearly-polarized light beam on passing through an optically active substance in the spectral region corresponding to the optically active absorption band becomes elliptically polarized. This phenomenon, which is intimately connected with the rotation of the plane of polarization, is called **circular dichroism.** Instruments have been developed recently, so-called dichrometers, which record circular dichroism curves against wavelength (in the same way as curves of ordinary absorption are recorded).

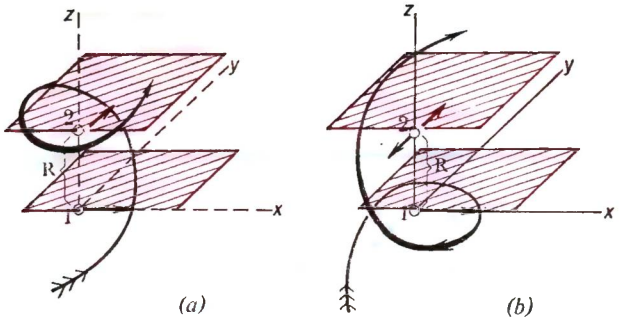
Circular dichroism curves (CD curves) provide, in general, the same information as ORD curves, but owing to their disposition (they are concentrated near the corresponding optically active absorption bands), CD curves are often more easily interpreted and correlated to the specific structural features of a substance than ORD curves.

### 4.9.4. PHYSICAL THEORIES OF OPTICAL ROTATION

The physical theory of optical rotation must provide an answer to the question: Why does circular birefringence (the absorption coefficients for the two circularly polarized components are different) and, hence, optical activity, arise? The answer to this question can be found by considering the interaction between light and matter.

The first attempts to develop a physical model of optical activity on the basis of the electromagnetic theory of light were made by Drude. His idea was that in an optically active substance an electron is displaced along a helical path. Drude showed that such a "helical electron" must respond differently to the action of the left- and right-circularly polarized rays, which is what accounts for the origin of optical activity. Though W. Kuhn showed later that there was a calculation error in Drude's work and that upon its elimination the model of the helical electron, as calculated by the classical laws, would not give optical activity, the idea of the helical motion of electrons forms the basis of modern quantum-mechanical calculations of optical activity.

Figure 4.11.




*The Kuhn model of interconnected oscillators (1 and 2 = electrons).*

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The next step in the development of the physical theory of optical activity was the works of Born, which were developed and detailed by Kuhn, who worked out his own model of optical activity (96). According to Kuhn, the simplest model of an optically active molecule must contain two interacting electrons (or two electronic systems) capable of vibrating in two mutually perpendicular directions. Between the two electronic vibrations there must exist an interaction which reveals itself in that the displacement of electron *1* (Fig. 4.11) in the positive direction along the *x*-axis causes electron *2* to shift in the positive direction along the *y*-axis. This model reacts differently to the action of the left- or right-circularly polarized wave.

In Fig. 4.11 the arrows *1* and *2* show the displacements of electrons, which result due to an interaction of the type indicated. In the case shown in Fig. 4.11, the circularly polarized wave displaces electron *1* in the positive direction along the *x*-axis and thus causes, by way of "induction", a positive displacement of electron *2* along the *y*-axis. The displacement of electron *2* caused by the action of the circularly polarized wave depends on its sign: the left-circularly polarized wave (Fig. 4.11*a*) approaches electron *2* in such a phase that it will displace the electron to the right along the *y*-axis (i.e., the action of the wave and the "effect of induction" add up together), and the right-circularly polarized component (Fig. 4.11*b*) will tend to displace electron *2* in the negative direction along the *y*-axis (the action of the wave and the "effect of induction" cancel out). Thus, the field of the light wave in the second case will perform an additional work against the forces that cause the positive displacement of electron *2* in the given model. As a consequence, the two circularly polarized components will travel with different velocities and, hence, the refractive indices will be different, $n_L \neq n_R$, i.e., optical rotation will result.

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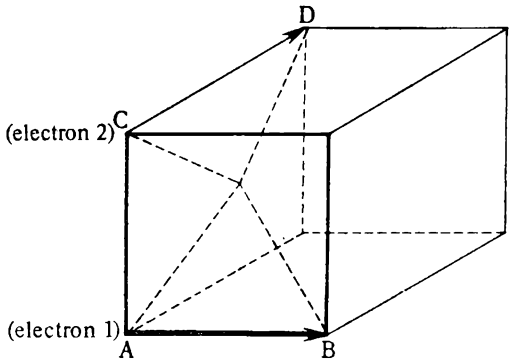
Figure 4.12.




*Comparison of the Kuhn model with the asymmetric atom (the arrows show the preferred directions of vibration of electrons* 1 *and* 2*).*

The model may be extended to any (not only perpendicular) angles between the directions of the inducing vibration and the vibration caused by it, and to any distance between electrons (and not only $\lambda/4$, as assumed in the drawing for the sake of clarity). It may seem that the Kuhn model assumes the existence of an optically active *diatomic* molecule since we were dealing with the interaction between two electronic oscillators. But this is not so; it is necessary that other structural elements be present in order to create for the oscillators the preferred directions of vibrations adopted by us. With this circumstance taken into account, the model must have, for example, the form shown in Fig. 4.12.

The atom B is responsible here for the preferred vibrations of the oscillator A in the direction AB, and the atom D for the preferred vibrations of the oscillator C in the direction CD. The four atoms here form a non-planar asymmetric structure, which is in agreement with the conceptions of the tetrahedral asymmetric carbon atom. The fifth atom, an asymmetric centre itself, is required for chemical reasons, only as a linking centre for the four substituents. Models have been devised at present, which do not contain such a central atom (see page 394 concerning optically active compounds of the adamantane series).

The mathematical inference, according to Kuhn, leads to the dependence of optical rotation on two parameters: the anisotropy factor $g$ and the power of the oscillators $f$. The positive aspect of these parameters is that they can be found from experimental data. The aniso-

tropy factor $g$ is determined from circular dichroism curves ($\varepsilon$ is the absorption of unpolarized light):

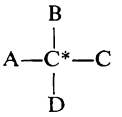
$$g = \frac{\varepsilon_L - \varepsilon_R}{\varepsilon}$$

The values of $f$ are calculated from the intensity of the corresponding optically active absorption bands.

Since absorption bands are caused by the presence in the molecule of special groups (chromophores), on which there is extensive spectroscopic material in the literature, the Kuhn approach allows one to predict optical activity on the basis of a knowledge of the UV spectra of the corresponding compounds with account of the relative position of the chromophore and the asymmetric centre.

The general physical concepts considered above were successfully applied to concrete cases in the joint works of Kuhn and Freudenberg. In an article published in 1933, Freudenberg considered in detail the semi-quantitative regularities of optical rotation in the light of the Kuhn theory (97).

If in the compound

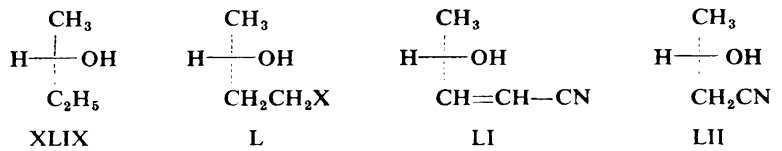


neither of the four groups attached to the asymmetric centre has absorption bands in the near UV region, the rotation $[M]$ observed will be relatively small. Such a case may be encountered among the aliphatic alcohols (the absorption band of the hydroxyl group lies at about 180 nm, in the far UV region). But if at least one of the groups linked to the asymmetric centre absorbs in the near UV region (the carbonyl group, the phenyl group, etc.), then the rotation in the visible region of the spectrum attains, as a rule, a considerable value. In accordance with the Chugaev rule, it is also important that the absorbing group be close to the asymmetric centre.

The effect of the absorbing group becomes particularly pronounced when there are no other groups that absorb in the near UV region. Thus, for 2-halohexanes the molecular rotation increases in the sequence Cl < Br < I, i.e., as the absorption band approaches the visible part of the spectrum (98).

The role of the aromatic absorption band is illustrated by a comparison of the following pairs: phenylmethylcarbinol has $[M_D]$ 63°, cyclohexylmethylcarbinol, 9°; mandelic acid, 240°, and hexahydromandelic acid, only 40°.

Optical rotation depends on the relative position in the molecule of the centre of asymmetry and the chromophore which is responsible for the appearance of an optically active absorption band. Thus, the Kuhn theory provided a physical substantiation of the Chugaev Distance Rule (see page 279) worked out long before the theory was enanciated. As an example, Kuhn used data on the optical activity of carbinols containing absorbing substituents in different positions. For carbinols of configuration XLIX and their derivatives with the second substituent remote from the asymmetric centre (compound L) there is observed a right-handed rotation. But if the substituent with a new absorption band is situated closer to the asymmetric centre (in the β-position, see page 280), then the sign of rotation is reversed for compounds LI and LII — these compounds are levorotatory.




X=Br, $CONH_2$, COOH, $CH=CH_2$ $CH=C(CH_3)_2$

Based on their own investigations, Kuhn and Freudenberg formulated the so-called **vicinity rule,** according to which the substitution-induced changes of rotation arise due mainly to the changes of the anisotropy of the absorption band of the group replaced and are, only to a small extent, caused by a change of the influence of the given group on the other substituents. Kuhn and Freudenberg coined the term **vicinal action** for the above-mentioned effect on other substituents.

A classical example that illustrates the vicinal effect (or vicinal action) is the comparison of the ORD curves of the methyl ester of α-azidopropionic acid (methyl α-azidopropionate) with that of the dimethylamide of the same acid, which was made by Kuhn and Freudenberg (99). At present, owing to the extensive progress of spectropolarimetry, examples of this kind can be easily found in many works, but we shall not consider them in detail.

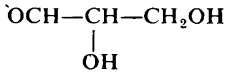
To sum up, it is important to emphasize once again that from the physical viewpoint, optical activity results from the interaction of two factors: the absorption band due to the chromophore and the chiral centre which renders this absorption band anisotropic (optically active).

It is fundamentally important that the optical activity of the corresponding chromophore can be induced not only by the ordinary intramolecular effect of the chiral centre but also by the presence of an optically active environment — by the effect of an optically active solvent (100). This has been proved by the appearance of optically active

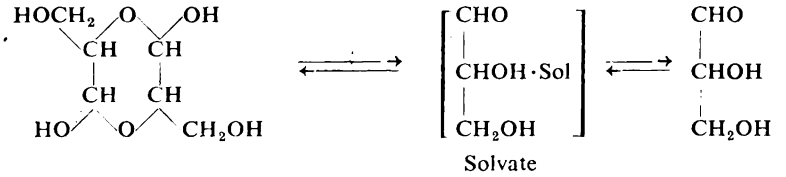
absorption bands in benzophenone or hexammine cobalt (II) perchlorate dissolved in D-diethyl tartrate or L-butane-2,3-diol in acetone under the action of (—)-menthol.

Beginning from the middle of the fifties, when wide use was made of measurements of ORD and then of CD, extensive material has accumulated, which directly confirm the validity of the conceptions advanced by Kuhn and Freudenberg and which at the same time deepens and details them. Of the large body of experimental data generalized in a number of books (101) we shall cite only a few examples which refer to the aliphatic compounds under consideration.

Glyceraldehyde



has an absorption band at 290 nm characteristic of the carbonyl group. This absorption band is optically active: the circular dichroism maximum is also situated at 290 nm. A careful study of CD has enabled the detection of phenomena that have remained unnoticed on the UV spectra: on passing from aqueous solutions to solutions in dioxan, dimethyl sulphoxide, or dimethylformamide, there appears a second optically active absorption band at 330 nm. This is accounted for (102) by the coexistence of three forms of compounds in the solutions—the dimeric, and the solvated and unsolvated monomeric forms:

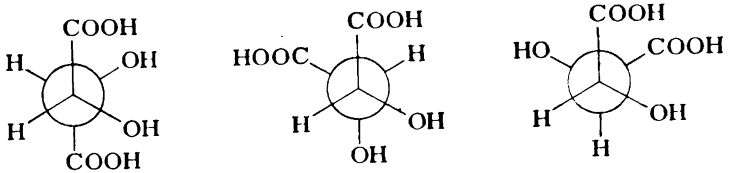



The CD spectrum of another simple aliphatic compound, S-(+)-lactic acid, has a negative maximum in the region of 240-250 nm; it is probably associated with the $n \rightarrow \pi^*$ transition in the carboxyl group since it disappears on leaching (103).

### 4.9.5. OPTICAL ACTIVITY AND CONFORMATION

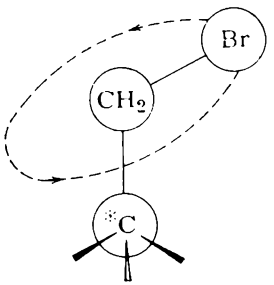
Many investigators have long attempted to account for certain phenomena associated with optical activity by the concept of dynamic isomerism, i.e., by the presence, in liquid optically active substances (or in solutions), of several forms, the equilibrium between which varies, depending on the external conditions. The various assumptions have been made concerning the nature of these forms: the association of

the optically active substance itself, the formation of associations with the solvent (solvates). A different explanation was put forward in 1930; to interpret the complex dispersion of tartaric acid, an assumption was made of the existence in it of three conformations, each of which makes a certain contribution to the rotation observed:




Such conceptions of the nature of "dynamic isomers" were later confirmed by physicists. Calculations have shown that the rotation value must depend substantially on the conformation of a molecule. As an example, let us consider the work of Kauzman and Eyring (104), who proceeded from the Kuhn conception of the relation between optical rotation and definite absorption bands and, hence, definite functional groups (chromophores). The chromophore group itself, say, OH or Br, isolated from the effect of the asymmetric centre, cannot cause optical rotation, its absorption band being isotropic. The asymmetric centre near the chromophore renders the absorption band anisotropic: such an interaction is called by the authors the first-order vicinal effect, which introduces the corresponding first-order increment—a constituent part of the total observed value of optical rotation. A different type of interaction—the vicinal effect of the second order—consists of the effect on the chromophore that has already been perturbed by another group; this gives rise to second-order increments, which are inferior in magnitude to first-order increments.

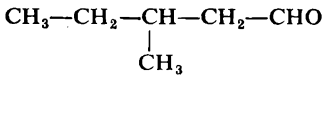
For further treatment the authors make use of the following scheme:



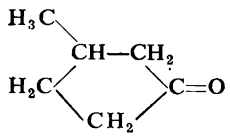

If free rotation about the $C_{asym}—CH_2$ bond is possible in the given model, then the time-averaged position of the chromophore (the bro-

mine atom) is found to be at the continuation of the $C_{asym}—CH_2$ line: the entire grouping has, on the whole, an axis of symmetry passing along the indicated bond and does not therefore produce a rotation increment of the first order. But if the bromine atom (or another chromophore in the β-position relative to the asymmetric centre) is incapable of rotating about the $C_{asym}—CH_2$ bond (if a definite conformation is fixed), the entire grouping acquires asymmetry and a first-order increment appears, which makes a considerable contribution to the rotation.

To verify their inferences, the authors compare the rotation of structurally similar aliphatic and cyclic compounds, for example:



$[M]_D = +9°$

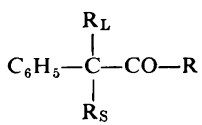


$[M]_D = +130°$

According to what has been said, the value of rotation in the cyclic compound is much higher. Especially considerable changes of rotation on cyclization are observed when this process is accompanied by a critical change in the conformation (105).

A very clear-cut proof of the role of conformational factors in optical rotation is the increase of the rotation of conformationally mobile compounds with decreasing temperature. The point is that at ordinary temperatures several conformers are usually at equilibrium, the rotation of which may be opposite in sign and, as a result of this, the total rotation is small. As the temperature falls the conformational equilibrium is increasingly displaced in favour of the most preferred conformer with a characteristic rotation. An example is 2-butanol (106).

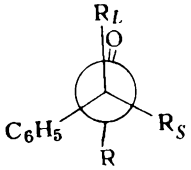
The relation between conformation and optical rotation has been studied for ketones of the type LIII ($R_S$ and $R_L$ are the small and large substituents at the asymmetric centre) (107).



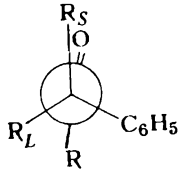
LIII

There exist two conformations in which the phenyl and carbonyl groups are in a position close to the skew position; it is precisely in these conformations that the above-considered condition for the creation of the asymmetry of the chromophore is most fully satisfied, and therefore these two conformations make principal critical contributions

to rotation. One of them (LIV) gives rise to a positive and the other (LV) to a negative Cotton effect:



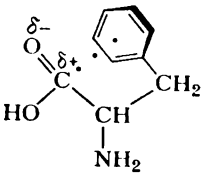

LIV




LV

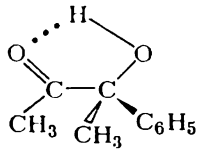
Conformation LIV is more preferred since the radical R, the benzene ring and the *least* bulky substituent at the asymmetric centre, $R_S$, are closer to one another. It is for this reason that ketones of configuration LIV have a positive Cotton effect, the amplitude of which is the higher the greater is the difference in the size of substituents $R_L$ and $R_S$ attached to the asymmetric centre.

Phenyl-substituted amino acids have considerably larger amplitudes of the Cotton effect than the corresponding alkyl analogues; the assumption has been made that this is the result of the creation of the fixed conformation held by the electrostatic attraction between the phenyl ring and the carbonyl group (108). For example:

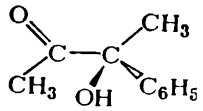



Such an interaction which takes place not along the carbon chain but directly through space has come to be known as **homoconjugation.** This interaction reveals itself not only on ORD curves but also on UV spectra (see also page 492).

The changes in the circular dichroism spectra of compounds in which the intramolecular interaction of two functional groups is possible have been accounted for by conformational factors (109). One of the compounds studied was S-(+)-3-hydroxy-3-phenyl-2-butanone, which can exist in conformations LVI and LVII:




LVI



LVII

Conformer LVI with an intramolecular hydrogen bond predominates in non-polar solvents (heptane, carbon tetrachloride); an intensive positive signal is observed on the circular dichroism spectra (the molecular ellipticity $[\theta]_{283} = +36{,}100$); the existence of an intramolecular hydrogen bond is confirmed by infrared spectra. Besides, the CD spectrum contains a very weak negative signal ($[\theta]_{317} = -1700$), which is probably associated with the presence of traces of conformer LVII. When use is made of solvents that break the intramolecular hydrogen bond, the negative band becomes predominant (in methanol $[\theta]_{268} = +4220$ and $[\theta]_{306} = -13{,}000$), which is associated with the shift of the conformational equilibrium to the side of the form LVII. An additional confirmation for such an interpretation is the fact that S-(—)-3-methoxy-3-phenyl-2-butanone, which is incapable of forming an intramolecular hydrogen bond, has a negative CD band, both in heptane ($[\theta]_{302} = -17{,}000$) and in methanol ($[\theta]_{300} = -12{,}600$).

### 4.9.6. BREWSTER'S CALCULATION OF OPTICAL ROTATION

Since the beginning of the study of optically active substances, numerous attempts have been made to devise a method for calculating optical activity on the basis of molecular parameters or at least to learn how to predict the sign of rotation. A thorough analysis of these works is given in the book "Foundations of Stereochemistry" by Terentiev and Potapov.

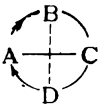
At the end of the fifties Brewster suggested an approach to the calculation of the sign and magnitude of optical rotation based on the consideration of two independent contributions, which are jointly responsible for the rotation observed:

(a) the configurational contribution, the calculation of which may be based on a comparison of the polarizabilities of the groups surrounding the asymmetric centre;

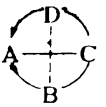
(b) the conformational contribution, the calculation of which may be carried out in different ways, depending on whether there are conditions in a compound for the creation of forms fixed by hydrogen bonds or there exists only an ordinary conformational equilibrium.

For the sign of the configurational contribution to be determined, Brewster proposed the following empirical rule. An asymmetric atom that has absolute configuration LVIII creates a right-handed rotation

if the polarizability of the substituents decreases in the sequences A > B > C > D (i.e., falls off in a clockwise direction). If the absolute configuration corresponds to formula LIX (the decrease of the polarizability of the substituents in an anticlockwise direction), then the rotation is left-handed.




LVIII

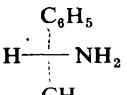



LIX

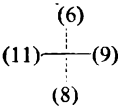
Groups that are often encountered as substituents at an asymmetric centre were arranged by Brewster in order of decreasing polarizability as follows:

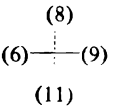
| (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) | (9) | (10) | (11) | (12) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| I | Br | SH | Cl | CN | $C_6H_5$ | COOH | $CH_3$ | $NH_2$ | OH | H | F |

For instance, in the case of α-phenylethylamine of configuration LX we replace the groups in the formula by their serial numbers and transform the formula in such a manner that the substituent with the highest polarizability is at the left:




LX



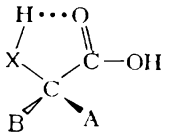




LXa

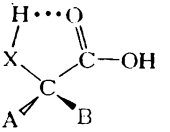
In the transformed formula LXa (to derive it from formula LX we naturally made use of only those manipulations which do not change the configuration; see page 48) the polarizability decreases in a clockwise direction—this corresponds to the right-handed rotation. From the works devoted to configuration determinations it is known that projection formula LX does represent the dextrorotatory α-phenylethylamine (see page 188).

This rule is valid for compounds having "pure atomic asymmetry", i.e., for those compounds in which the asymmetric atom is not part of a ring or a mobile chain capable of assuming various conformations. If the substituents can interact with one another, it is then necessary to take into account the factor of conformation fixation. For α-hydroxy and α-amino acids the sign of this correction corresponds to the follow-

ing schemes [X = oxygen (for hydroxy acids) or the NH group (for amino acids); A = substituent the polarizability of which is greater than that of B]:

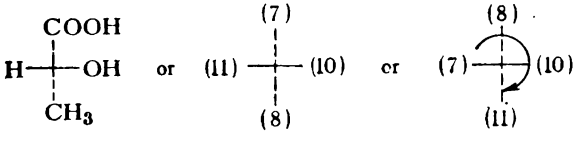



Conformation with (−)-contribution

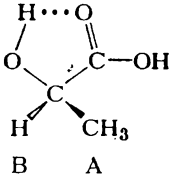



Conformation with (+)-contribution

In particular, for lactic acid LXI and alanine both contributions to optical rotation, the configurational and that determined by the fixed conformation, are opposite in sign, which is why their sum, i.e., the observed rotation, is relatively small and has an indefinite sign (varies depending on the solvent and concentration).




LXI LXIa

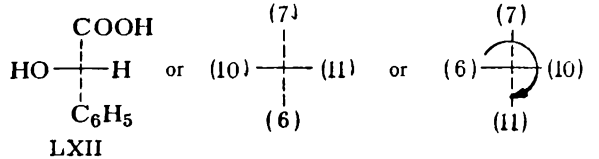



LXIb

(+)-Contribution (−)-Contribution

Atomic asymmetry introduces a (+) contribution to the rotation of lactic acid (LXa, the clockwise decrease of the polarizability of the groups); the fixed conformation factor makes a (—) contribution (LXb). The observed molecular rotation for lactic acid, $[M]_D$ with the configuration indicated by formula LXI is equal to —3°. Analogous reasoning may be used for alanine.

With dextrorotatory mandelic acid LXII both contributions are dextrorotatory; therefore one can predict with certainty the sign of rotation and anticipate a considerable magnitude of rotation.

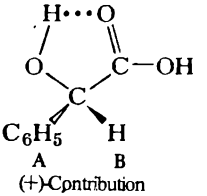



LXII

(+)-Mandelic acid

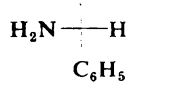
$[M]_D^{exp} = +243°$

(+)-Contribution




(+)-Contribution

The analogous result is obtained by considering phenylglycine which may be represented by projection formula LXIII:

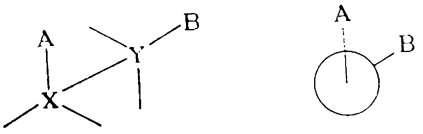



LXIII

(+)-Phenylglycine

$[M]_D^{exp} = +254°$

In the case of compounds in which the asymmetric centre is part of the chain capable of creating various conformations Brewster takes into account the conformational factor as well. We shall not consider the original approach to the calculation of the conformational factor because in a later publication (110) Brewster modified his approach to the calculation. The starting point in his reasoning is the models of optically active molecules proposed by Kauzmann and also by Tinoko and Woody. However, according to Brewster, these models are not simple enough mathematically to be understandable to the organic chemist. In his model Brewster makes use of the vivid conception of the motion of electrons along a "spiral homogeneous conductor" and on this basis derives calculation formulas relating the value of rotation to the length of the "conductor" (the bond length) and its electromagnetic properties (the polarizability of the groups forming the helix). Considering the configurational contribution to be negligibly small in his new work, Brewster concentrates all his attention on the calculation of conformational asymmetry. The helical fragments on the basis of which the calculation is made are the following skew conformational units:




LXIV

Here A and B are terminal substituents of the unit and X and Y are central atoms along the bonds of which the molecule is viewed in the Newman projection (usually these central atoms are saturated carbon atoms).

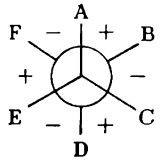
For the contribution of one skew conformational unit to be calculated, it is necessary to know the A—X, X—Y, and Y—B bond lengths,

which we denote as $d_1$, $d_2$, $d_3$, respectively, and also the refraction of the system, $\Sigma\Delta R_D$, which is the sum of the refractions of the bonds (according to Vogel). The contribution of a skew conformational unit is calculated by the formula:

$$[\Delta M_D]_{AB} = 251 \times \frac{d_1 d_2 d_3}{(d_1 + d_2 + d_3)^2} \left(\sum \Delta R_D\right)$$

Each conformation around the X—Y bond contains (in those cases when X and Y are, as usual, saturated carbon atoms) six skew conformational units. The calculated rotation of a pure conformer is equal to the sum of the contributions of these six conformational units, the signs of which alternate as follows:

$$[\Delta M_D]_1 = [\Delta M_D]_{AB} - [\Delta M_D]_{BC} + [\Delta M_D]_{CD} - [\Delta M_D]_{DE} + [\Delta M_D]_{EF} - [\Delta M_D]_{FA}$$




For the value of rotation of a substance to be calculated one has to compute the sum of the contributions of individual conformers ($[\Delta M_D]_1 + [\Delta M_D]_2 + [\Delta M_D]_3$) with account taken of their contributions to the conformational equilibrium ($n_1$, $n_2$, $n_3$):

$$[M_D] = n_1[\Delta M_D]_1 + n_2[\Delta M_D]_2 + n_3[\Delta M_D]_3$$

Besides, a correction is usually introduced for the refractive index of the medium in which the rotation has been determined. The correction factor $f(n)$ is calculated by the formula:

$$f(n) = \frac{(n^2 + 2)^2}{9n}$$

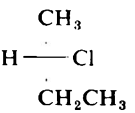
The correction factor $f(n)$ usually differs little from unity, therefore the correction for the refractive index may change the calculated values at least by 30-50 per cent, which is of no significance in calculations which are semiquantitative in most cases. Further simplifications are often introduced: one of the three possible conformations is rejected as an obviously unfavourable one, and the contributions of the remaining two are considered to be equal.

In his calculations Brewster uses the bond lengths given below (these bond lengths have been calculated on the basis of atomic radii according to Pauling and differ somewhat from the average experimental values given in Table 1.1; see page 18):

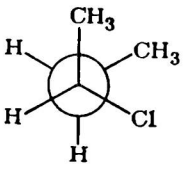
| Bond | Bond length, Å | Bond | Bond length, Å |
|---|---|---|---|
| C—C | 1.53 | C—F | 1.37 |
| C=C | 1.33 | C—Cl | 1.78 |
| C≡C | 1.21 | C—Br | 1.92 |
| C—H | 1.10 | C—I | 2.12 |
| C—N | 1.47 | N—H | 1.02 |
| C—O | 1.43 | O—H | 0.96 |
| C—S | 1.82 | S—H | 1.34 |

To facilitate the calculations, Brewster gives a table of rotation values for conformational units (Table 4.8), the use of which allows one to dispense with the calculation of the contribution of each of the conformational units (on the basis of the indicated bond lengths and bond polarizabilities according to Vogel by using the formula given on page 299) and reduces the calculation to the summation of the contributions of individual conformational units.

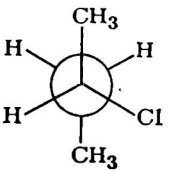
The use of the Brewster method is illustrated here by the calculation of the molecular rotation of (+)-2-chlorobutane which has the configuration



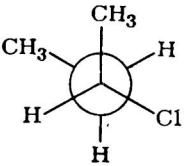

According to the data obtained by Pentin and coworkers (see page 234), the contributions of the individual conformers in liquid 2-chlorobutane are as follows (in molar fractions):



0.17

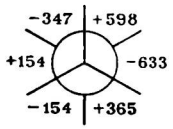


0.56



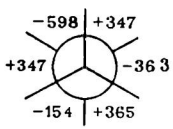
0,27

Using the data of Table 4.8, we calculate the rotation of each of the conformers as the algebraic sum of the contributions of the individual skew conformational units:




−17°

+73°




−56°

$[M]_D = 73 \times 0.56 - 17 \times 0.17 - 56 \times 0.27 = 22.8$

Considering that the $n_D^{20}$ value of 2-chlorobutane is about 1.40 and the value of $f(n)$ is equal to 1.24, we obtain the final result, $[M_D] = +28.2°$. It has been found experimentally that $[M]$ is about +30° (the exact value is unknown because of the uncertainty as to the optical purity of the preparations).

TABLE 4.8. THE ROTATIONS OF THE CONFORMATIONAL UNITS OF LXIV ACCORDING TO BREWSTER FOR THE D-LINE OF SODIUM

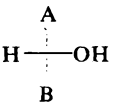
| A in formula LXIV | B in formula LXIV | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | H | F | OH | $NH_2$ | $CH_3$ | Cl | COOH | SH | Br | I | $C_6H_5$ |
| H | 154 | 159 | 225 | 297 | 347 | 365 | 405 | 480 | 483 | 698 | 1082 |
| F | | 168 | 240 | 319 | 376 | 398 | 436 | 528 | 531 | 775 | 1180 |
| OH | | | 314 | 395 | 453 | 478 | 515 | 609 | 615 | 860 | 1271 |
| $NH_2$ | | | | 477 | 537 | 566 | 600 | 700 | 707 | 957 | 1363 |
| $CH_3$ | | | | | 598 | 633 | 661 | 767 | 777 | 1037 | 1435 |
| Cl | | | | | | 672 | 699 | 813 | 823 | 1100 | 1509 |
| COOH | | | | | | | 727 | 824 | 844 | 1104 | 1501 |
| SH | | | | | | | | 956 | 971 | 1125 | 1648 |
| Br | | | | | | | | | 988 | 1270 | 1669 |
| I | | | | | | | | | | 1570 | 1945 |
| $C_6H_5$ | | | | | | | | | | | 2275 |

The calculation according to Brewster has also been successfully used for other compounds of the type $CH_3$—CHX—R, where R is the flexible carbon chain, and X is the rigid functional group. The results however are not good for compounds in which X is the hydroxyl or amino group. The model is inapplicable to compounds in which the chromophore groups are not conformationally free, which especially

refers to the phenyl group. Nonetheless, the Brewster rule has been successfully applied to 1-amino-1,2-diphenyl-3-propanols and related compounds (111). It has proved to be inapplicable to vicinal dibromides (112).

The calculation according to Brewster has been employed for the prediction of the absolute configuration of compounds with an asymmetric phosphorus atom (113).

A number of rules for special cases have been proposed. One of these rules, which is also associated with the name of Brewster (114), is called the benzoate rule. It states that alcohols of the configuration




(where the A group is less bulky than the B group) give benzoates, the rotation of which is positive. An analogous rule has been suggested for the dibenzoate derivatives of 1,2-glycols (115).

The CD sign of α-chloro- and α-bromoalkylcarboxylic acids obeys the "quadrant rule" (116), one of the versions of the Octant Rule which will be discussed at a later time (see page 394). There have also been proposed rules which relate configuration and conformation to optical rotation for nitro esters (117) and α-diketones (118).

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CHAPTER 5

# Stereochemistry of Ring Compounds

As has already been mentioned, the stereochemical features of cyclic compounds are first of all determined by two factors: the existence of various gradations of conformational mobility (which depends, in particular, on the number of members in the ring) and the simultaneous manifestation of two types of spatial isomerism, geometrical and optical. Thus, all the three principal stereochemical phenomena—conformational interconversions, and geometrical and optical isomerism—must be invariably taken into account in considering ring compounds.

Ring systems are usually classified, according to the number of members in the ring, into four groups: **small rings,** 3- and 4-membered; **common rings,** 5-, 6-, and 7-membered; **medium rings,** 8- to 11-membered; **large** or **macro rings,** 12-membered and larger. Small and common rings are often jointly classified under the name of classical rings, and medium and large rings as many-membered rings. Of great interest are also the various bi- and polycyclic (multi-ring) structures.

## 5.1. TYPES OF STRAIN IN RINGS

By the end of the seventies of last century, apart from compounds of the aliphatic series, which have an open chain of carbon atoms, there had become known cyclic compounds. These were benzene and its homologues, the products of their hydrogenation and also compounds of the cyclopentane series. Rings with a different number of members were not known; this led Meyer in 1875 to suggest that 5- and

6-membered rings were the only ones capable of existence. In the eighties of last century, however, the situation changed. In 1881 Markovnikov synthesized a compound with a four-membered ring: cyclobutane-1,2-dicarboxylic acid (cyclobutane itself was obtained much later, in 1907, by Willstätter), and in 1882 Freund prepared cyclopropane.

A big contribution to the study of the synthesis and properties of cyclic compounds was made by Perkin in the eighties and nineties of last century (Perkin was a young chemist at the time and worked in the von Baeyer laboratory). To synthesize polymethylenes Perkin used the then recently discovered method of malonic ester synthesis.

Comparing the facts known by that time, Baeyer advanced in 1885 his famous **strain theory.** According to Baeyer, when closed chains or rings are formed, the valence bonds of carbon atoms become diverted from their normal tetrahedral direction, the amount of this departure depending on the number of members in the ring. Thus, for example, cyclopropane must be an equilateral triangle, in which the angle between the ring-forming bonds of the carbon atom must be 60° and not 109°28′ as is the case in a regular tetrahedron.

In a general form, the angle of departure, $\alpha$, can be calculated from the formula:

$$\alpha = \frac{1}{2}\left[109°28' - \frac{2(n-2)}{n} \times 90°\right]$$

where $n$ is the number of members in the ring.

The deviation of valence bonds from their normal direction in the tetrahedral model of the carbon atom is the greatest, as calculated according to Baeyer, in three-membered rings; it decreases with increasing number of members and reaches a minimum in five-membered rings. Further, beginning from six-membered rings this departure begins increasing again, but the valence bonds are no longer brought closer together, as is the case in small rings, but are diverging.

By analogy with rings, it is possible to calculate the magnitude of the angle of departure in the formation of a double bond (54°44′) and a triple bond (70°32′).

The main idea of the Baeyer strain theory is that the magnitude of the angle of departure of valence bonds must be associated with the internal energy of the molecule: the greater the departure the higher is the energy reserve and the lower the stability of the ring. From thermochemical data it is known that the energy of small rings does change qualitatively in the same direction as the strain calculated according to Baeyer. In the case of six-membered rings, however, the heat of combustion points to the absence of any strain, which does not agree with the Baeyer calculation. Medium and large rings, which must have been strongly strained according to Baeyer, also prove to be quite stable.

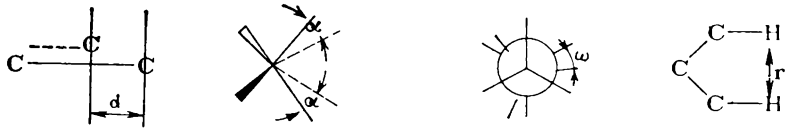
Attempting to eliminate this contradiction, Sachse in 1890 advanced a correction to the Baeyer theory. He suggested that all rings, beginning from six-membered rings, can be built without distorting the carbon tetrahedron, and therefore there is no angle strain in them. For such models to be built, the planar structure of rings, which was proposed by Baeyer, must be rejected. Thus, for example, for cyclohexane Sachse proposed two strainless forms—the boat and chair conformations.

The conceptions of the non-planar structure of rings were later fully confirmed. It was also found that the distortions of bond angles considered by Baeyer is only one of the possible factors responsible for strain in molecules (for a detailed review, see ref. 1). Hendrickson (2) proposed the following method of calculation with account being taken of four factors which may increase the internal energy of the molecule.

1. The **Baeyer strain** (also known as *angle strain* or *classical strain)*—the alteration of the bond angles. This strain is proportional to the square of the angle of deviation ($\alpha$) of the valence bonds from their normal tetrahedral structure: $E_1 = K_\theta \alpha^2$. With the usually adopted value, $K_\theta \approx 0.0840$, this gives 0.33 kJ/mole for a deviation of 2°; about 9 kJ/mole for a deviation of 10°, and 34 kJ/mole for a 20° departure.

2. The **bond strain**—the alteration of the interatomic distances, i.e., the stretching or compression of chemical bonds. A mathematical expression for strain of this kind is given by the function $E_2 = kd^x$, where $d$ is the amount of linear displacement of the atom from its normal position. The exponent $x$ is much greater than unity and so $E_2$ is a steep potential function; the changes in the normal interatomic distances occur with great difficulty.

3. The **eclipsing strain** *(torsional strain, Pitzer strain)*—the forced deviation from the most favourable staggered conformation. The energy is expressed by the function $E_3 = 5.87\ (1 - \cos 3\omega)$:




where $\omega$ is the amount of deviation of the dihedral angle from its most favourable staggered state.

4. **Prelog strain** *(steric strain)*—the intramolecular van der Waals forces—the steric repulsion between closely spaced atoms (mainly, hydrogen atoms; $r$ is the distance between non-bonded hydrogen atoms):

$$E_4 = 4.19(10^{4-3r} - 49.2r^{-6})$$

Any molecule, in particular, a cyclic molecule, tends to assume such a conformation in which the sum $E_1 + E_2 + E_3 + E_4$ is minimal. The energies of simple molecules, say, cyclohexane, have been calculated by means of electronic computers for different conformations. These calculations have shown that a satisfactory agreement with experiment can be arrived at with the aid of the formulas given above. For a theoretical treatment of the energy of alicyclic compounds and the conformational notation, the reader is referred to the works by Dunitz and Waser, and Shaw (3).

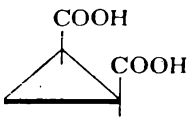
A detailed study of ring conformations is one of the most important aspects of the stereochemistry of cyclic compounds. With substituents (side chains) being present in rings, however, apart from the problem of the conformation of the ring itself, the investigator is faced with the problems of the *configuration of substituents*. It is the latter problem that is considered first, so that further in the treatment of material on concrete cyclic systems we may speak of them as a combination of the ring itself and the substituents.

## 5.2. CONFIGURATIONS OF SUBSTITUTED RINGS

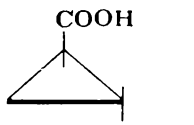
In establishing the configurations of cyclic compounds, use may, in general, be made of the methods that have already been considered in this book (see Chapter 3): the methods of determining the configurations of chiral molecules if the configurations of optical antipodes (enantiomers) are to be elucidated, and the methods of determining *cis-trans* configurations if we speak of the position of substituents relative to one another and to the ring.

The concept of the *cis-trans* configuration has sense only in application to saturated small rings: in rings possessing a larger number of members the mobility becomes so great that we cannot speak of the *cis-* or *trans*-position of a pair of substituents. In the case of 6- to 8-membered rings, *cis-trans* isomerism manifests itself in peculiar forms which will be examined in discussing the appropriate rings.

For the *cis-trans* configuration of substituents to be determined, use is often made of the **method of cyclization** which is already familiar to us. A classical example is the stereoisomeric cyclopropane-1,2-dicarboxylic acids. There exist two stereoisomeric acids: one of them, which has m.p. 139°C, is capable of forming a cyclic anhydride and is thus the *cis*-isomer. The other stereoisomeric acid with m.p. 175°C does not form a cyclic anhydride; this is the *trans*-isomer.

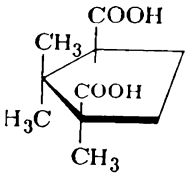



*cis-*

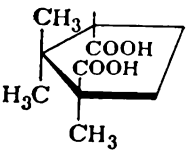



*trans-*

The same relations are observed with two stereoisomeric 1,2,2-trimethylcyclopentane-1,3-dicarboxylic acids. One of these acids, camphoric acid, m.p. 187°C, forms an anhydride with m.p. 222°C and is thus the *cis*-isomer. The other one, isocamphoric acid, which has a melting point of 171°C, forms no anhydride; this is the *trans*-isomer.




*cis-*

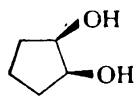



*trans-*

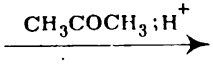
The *cis-trans* isomerism of cyclohexane-1,4-dicarboxylic (hexahydrophthalic) acids was observed by Baeyer in his classical works in the nineties of last century. The configurations were assigned to these acids by Baeyer only on the basis of the similarity to fumaric and maleic acids. Much later, in 1934, Malakhovsky decided to determine the configurations of these acids by means of the cyclization method, but, to his surprise, he obtained anhydrides from both stereoisomers. In subsequent years, these anhydrides were found to be polymeric and not cyclic: one of the anhydrides was converted into a true cyclic anhydride by vacuum distillation and this cyclic anhydride was subjected to hydrolysis to give the *cis*-isomer of the acid (m.p. 169°C). The second stereoisomer of cyclohexane-1,4-dicarboxylic acid, m.p. 310°C, is the *trans*-isomer. The configurations determined in this way proved the validity of the assumptions made by Baeyer, and no error was thus made. This example, however, deserves mention as a caution: the fact of anhydride formation cannot by itself serve as a proof of configuration without elucidating the nature of the resulting anhydride.

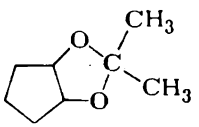
Other complications arise in the case of cyclohexane-1,2-dicarboxylic acids: because of the peculiar spatial form of the cyclohexane ring the two forms do give true cyclic anhydrides. This point will be taken up at a later time.

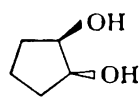
Ring formation (cyclization) was used in the works of Böeseken (1923) for the elucidation of the *cis-trans* configuration of cyclic glycols. Thus, of the two 1,2-cyclopentanediols only the *cis*-isomer is capable of forming a cyclic ketal with acetone.



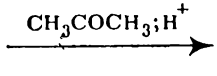

*cis-*, m.p. 48°C




*trans-*, m.p. 10°C

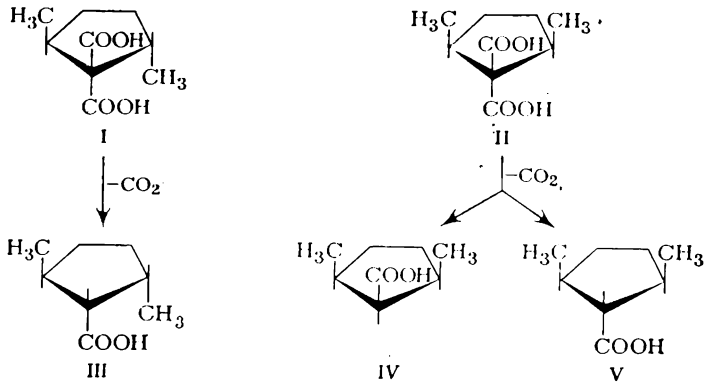



Does not react

The *cis*- and *trans*-cyclohexane-1,2-diols too differ in their behaviour towards acetone (only the *cis*-isomer gives a ketal), whereas the seven-membered ring turns out to be so mobile that both the *cis*- and *trans*-cycloheptane-1,2-diols are capable of forming acetone derivatives.

The configurations of 2-aminocyclopentanol has been determined by taking advantage of its ability to form complexes with cobalt chloride; a brightly coloured, stable complex compound is formed by the *cis*-form only (4).

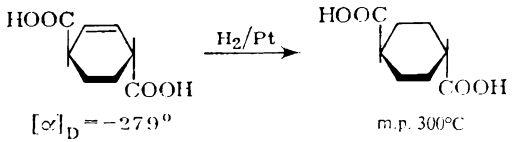
A peculiar method has been devised specifically for the determination of the configurations of cyclic compounds, which may be called the method of conversion into a compound of lower symmetry. For instance, in the decarboxylation of stereoisomeric 1,3-dimethylcyclopentane-2,2-dicarboxylic acids, the *trans*-isomer I gives only *one* monocarboxylic acid III, and the *cis*-isomer II forms two stereoisomeric monocarboxylic acids, IV and V, depending on which of the carboxyl groups is eliminated:



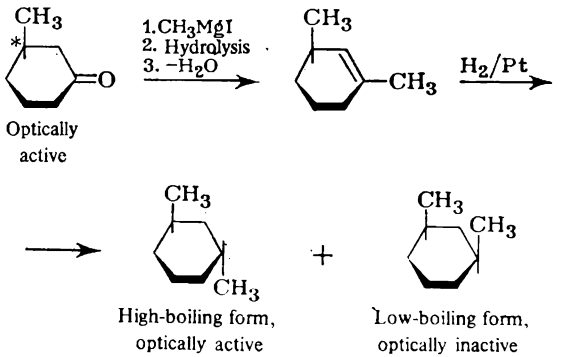

A reliable criterion in the determination of the *cis-trans* configurations of cyclic structures is the ability of disubstituted derivatives, with a certain definite arrangement of identical substituents, to be resolved into optical antipodes (enantiomers); we are speaking of the difference between the *meso*- and racemic forms, which has been considered in Chapter 3 (page 174).

The resolution into antipodes has been used, for example, to prove the configuration of stereoisomeric $\Delta^2$-tetrahydrophthalic acids and, through these, the configurations of hexahydrophthalic acids. Of the two stereoisomeric cyclohexenedicarboxylic acids only one was resolved into optical antipodes and was thus found to have the *trans*-configuration. The catalytic hydrogenation of this acid gives a hexahydrophthalic

acid with m.p. 309°C, the *trans*-configuration of which is thus unambiguously established (5):



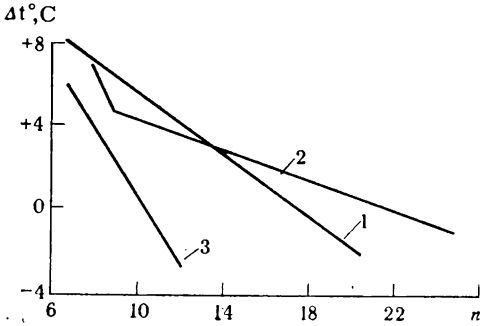

The preparation of one of the stereoisomers of 1,3-dimethylcyclohexane in an optically active form from optically active 3-methylcyclohexanone has shown that it cannot have the *cis*-configuration that was originally assigned to it on the basis of the Auwers-Skita rule (see below), and that it must have a *trans*-configuration:




An important auxiliary means in the determination of the configuration of cyclic compounds was the Auwers-Skita rule (6), which in its original form states: the *trans*-forms of dialkylcyclanes have lower boiling points, refractive indices and densities and higher molecular refractions than the *cis*-forms. The Auwers-Skita rule thus formulated has been successfully used to determine the configurations of simple cyclopentane derivatives that have methyl or ethyl groups as substituents. The Auwers-Skita rule in this formulation has however been found to be inapplicable to 1,3-disubstituted derivatives of cyclohexanes (7).

Moreover, it has turned out that the Auwers-Skita rule is applicable to other types of compounds only if the side chains are not too long (8). Figure 5.1 gives experimental data on the boiling points of stereoisomeric dialkylcyclanes. The straight lines which express the dependence of the difference between the boiling points of the *cis*- and *trans*-forms on the total number of carbon atoms in the molecule approach the horizontal axis. The points of intersection with this axis show the number of carbon atoms (different for dialkylcyclanes of different types) at

Figure 5.1.




*The difference between the boiling points of cis- and trans-isomers of dialkylcyclanes versus the number of carbon atoms in the molecule, n:*
1 — 1,2-*dialkylcyclopentanes*; 2 — 1,2-*dialkylcyclohexanes*; 3 — 1,4-*dialkylcyclohexanes*.

which the Auwers-Skita rule becomes invalid with respect to boiling points. Analogous graphs can be constructed for other constants — refractive indexes and densities of compounds. The inferences drawn on the basis of the relationship shown in Fig. 5.1 have been confirmed by experimental measurements of the constants of higher dialkylcyclanes.

At present the formulation of the Auwers-Skita rule has been changed; it states (9): in a pair of isomeric disubstituted cyclohexanes the isomer with the diequatorial orientation of substituents has the lower boiling point, refractive index, and density. The thus modified rule is also applicable to 1,3-isomers, isomeric methylcyclohexylamines (10) and other derivatives of cyclohexane.

A new approach to the rule of boiling points has been suggested by Kellie and Riddell (11). The authors make use of the following equation to express the boiling points of a series of structurally related compounds:

$$T_x = T_0 + \sum a$$

where $T_x$ is the boiling point to be calculated; $T_0$ is the boiling point of the parent member of the series; $\sum a$ is the sum of the increments which depend on the nature and number of substituents.

Thus, for example, the boiling points of methylated cyclohexanes can be calculated (see Table 5.1) by adding the following increments to the boiling point of cyclohexane (81.4°C):

| | |
|---|---|
| Equatorial $CH_3$ group | +19.1°C |
| Axial $CH_3$ group | +23.0°C |

The following must also be taken into account:

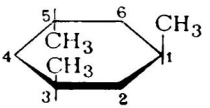
| | |
|---|---|
| Geminal $CH_3$ groups | −5.7°C |
| *ee*-Vicinal $CH_3$ groups | +4.2°C |
| *ea*-Vicinal $CH_3$ groups | +3.1°C |

TABLE 5.1. THE CALCULATED AND EXPERIMENTAL VALUES OF THE BOILING POINTS OF METHYLATED CYCLOHEXANES

| Compound | Boiling point, °C | |
|---|---|---|
| | calculated | experimental |
| Methylcyclohexane | 100.5 | 100.9 |
| *cis*-1,2-Dimethylcyclohexane (*ea*) | 126.6 | 129.7 |
| *trans*-1,2-Dimethylcyclohexane (*ee*) | 123.8 | 123.4 |
| *cis*-1,3-Dimethylcyclohexane (*ee*) | 119.6 | 120.1 |
| *trans*-1,3-Dimethylcyclohexane (*ea*) | 123.5 | 124.5 |
| 1*r*,2*c*,4*t*-Trimethylcyclohexane | 142.9 | 142 |
| 1*r*,3*c*,5*c*-Trimethylcyclohexane | 138.7 | 138.4 |
| 1*r*,3*c*,5*t*-Trimethylcyclohexane | 142.5 | 140.5 |

In those cases when the calculated and experimental values differ significantly, the authors consider the normal chair-like conformation of the cyclohexane ring to be distorted.

In Table 5.1, the configurations of trisubstituted rings are designated by using a system in which the *cis*- (*c*) or *trans*- (*t*) position of substituents is indicated relative to one of them, which is chosen as the reference (*r*) substituent. Thus, 1*r*,3*c*,5*t*-trimethylcyclohexane has the following structure:




A more limited rule (12) has been proposed specifically for 1,4-disubstituted cyclohexanes (12): the *trans*-forms (*ee*-) of 1,4-disubstituted cyclohexanes with identical substituents melt higher than the *cis*-forms (*ea*-).

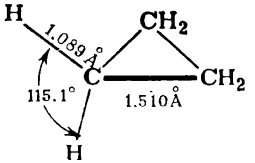
It has also been suggested that the values of the boiling point, density, and refractive index be used for estimating the "root-mean-square radius of the molecule" and for determining configuration and conformation on the basis of the radius values obtained (13).

To determine the configurations of cyclic compounds, wide use is made of the NMR and IR spectroscopic methods. The use of these methods is based on certain regularities which relate *conformation* to the pattern of NMR and IR spectra; the conformational features of a compound in their turn allow one to deduce its configuration. The relevant examples will be discussed at a later time.

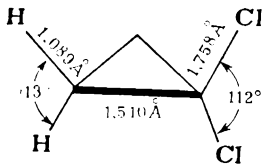
## 5.3. THREE- TO FIVE-MEMBERED RINGS

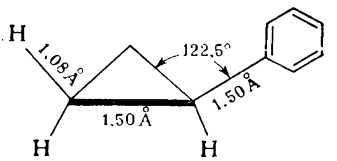
### 5.3.1. CONFORMATIONS

**Cyclopropane** is the only planar alicyclic compound (the three points invariably lie in a single plane). The geometric structure of cyclopropane is as follows according to the data of X-ray diffraction studies (14):

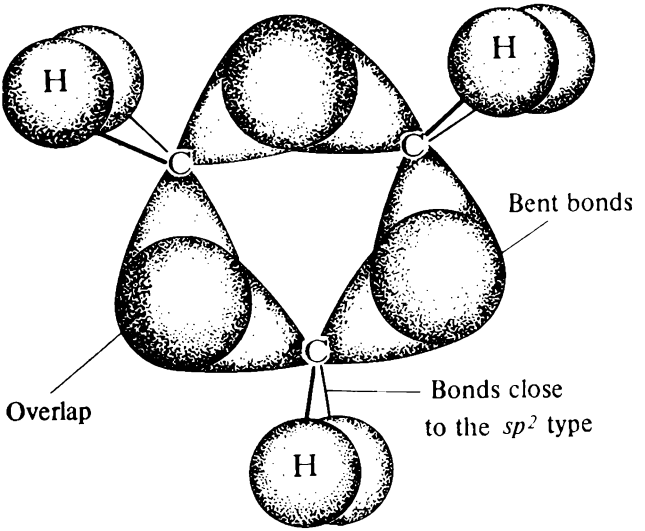



There are also electron diffraction data on the structure of 1,1-dichlorocyclopropane (15) and phenylcyclopropane (16):



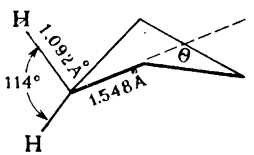



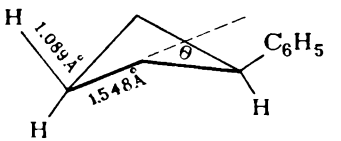

The most remarkable feature in these and other data is a certain contraction of the distance between the carbon atoms in the three-membered ring (1.51 Å instead of 1.54 Å in the aliphatic chain). At present this is considered to be one of the manifestations of the specific character of the bonds in the cyclopropane ring, of the so-called banana or bent bonds in cyclopropane.



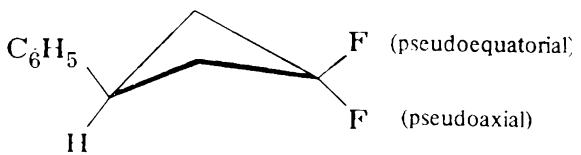
The interaction of the C=O double bond with banana bonds is believed to account for the cisoid conformation of the cyclopropane ring relative to the C=O group in the amide of cyclopropanecarboxylic acid, in cyclopropyl methyl ketone (17). The specific feature of these bonds is also manifested in the chemical behaviour of cyclopropane derivatives (see page 318). The conformations of compounds of the cyclopropane series have been calculated by Meyer (18).

**Cyclobutane** has no planar structure, in contradiction to the former conceptions. The geometric parameters of cyclobutane and phenylcyclobutane are as follows:

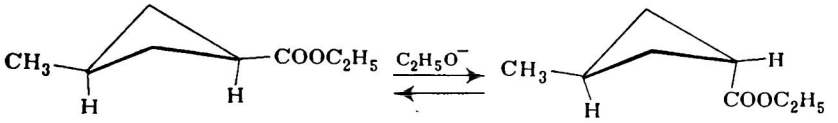



The puckering of θ is 20-25°. The non-planar structure of cyclobutane has been established by means of X-ray and electron diffraction methods, on the basis of dipole moment measurements, from the NMR spectra, and also with the aid of other methods. Thus, the $^{19}$F-NMR spectra of 3-phenyl-1,1-difluorocyclobutane point to the non-equivalence of the fluorine atoms since they are in the pseudoequatorial and pseudoaxial conformations:




The inference as to the non-planar conformation of the cyclobutane ring has also been made in the investigation of the thermodynamic equilibrium of the *cis-trans*-stereoisomeric esters of 3-alkylcyclobutanecarboxylic acids (19). If the cyclobutane ring had a planar structure, the *trans*-isomer, in which the interaction between the substituents is weaker, would be more stable. Instead, the *cis*-isomer was found to be the more stable and predominating in the thermodynamic equilibrium. This was accounted for by the fact that with the non-planar structure of the cyclobutane ring the two substituents in the *cis*-form are able to occupy the more favourable pseudoequatorial position, whereas in the *trans*-form one of the substituents will invariably be in the pseudoaxial position:

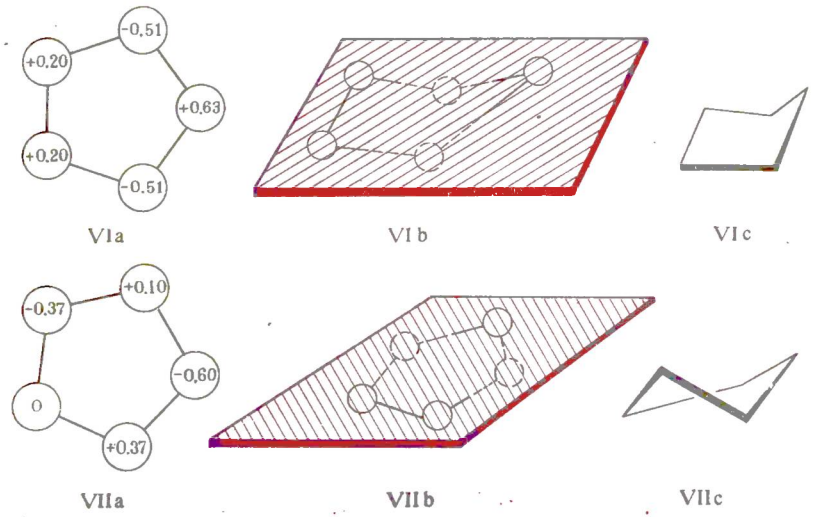



*cis-* *trans-*

The driving force responsible for the conversion of cyclobutane into the non-planar conformation is a decrease of the eclipsing strain (Pitzer strain). The conformations of cyclobutane derivatives, in particular, of cyclobutanones, have been considered in detail by Conia (20).

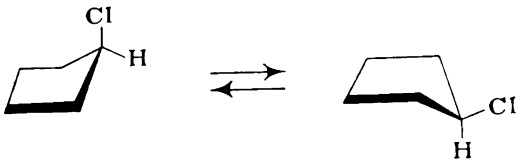
In the planar model of **cyclopentane,** the angle of departure of the valence bonds from their normal tetrahedral direction is less than 1° and therefore no Baeyer strain is present here. The Pitzer strain, the eclipsing of the five C—C bonds, should have caused an additional strain of about 63 kJ/mole in the planar conformation of cyclopentane. In fact, however, this strain energy falls down to 27 kJ/mole due to the change into the non-planar conformation.

Two non-planar conformations are believed to exist for cyclopentane: the envelope form VI and the half-chair form VII. Below are given three representations of these forms: in projections VIa and VIIa the numbers indicate (in angstroms) the amount to which the corresponding carbon atoms are twisted out of the plane of the drawing (the average plane of the ring); in VIb and VIIb the perspective projections onto this plane are given; VIc and VIIc are the conventional representations of these conformations.



The individual carbon atoms of cyclopentane do not occupy a rigidly fixed position relative to the average plane, i.e., the ring, as it were, is in constant wave-like motion, this effect being called pseudorotation. The barrier to pseudorotation is about 17 kJ/mole.

A consequence of the non-planar conformation of cyclopentane is the non-equivalence of the exocyclic valence bonds of its carbon atoms. As a result, the substituents in cyclopentane may occupy either the pseudoaxial or pseudoequatorial position. For example, in liquid chlorocyclopentane the two conformers are in equilibrium:




When the temperature decreases, the pseudorotation is retarded: at 77°K the molecule of chlorocyclopentane becomes "frozen" in an energetically more favourable conformation (21).

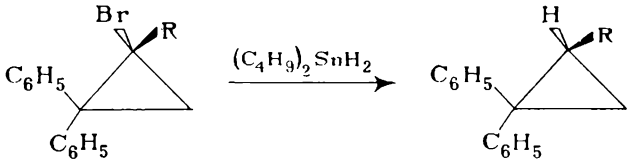
*cis*-1,3-Dimethylcyclopentane, which is capable of assuming the envelope conformation with two pseudoequatorial substituents, is energetically more favourable than the *trans*-isomer with its *ea*-orientation; the situation here is the same as in the cyclobutane derivatives considered above.

The carbon-carbon single bonds in cyclopentane (1.546 Å) are somewhat longer than those in alkanes (1.533-1.534 Å), which is accounted for by the repulsion of the transannular type since the distance between the non-bonded carbon atoms in cyclopentane (2.444 Å) is smaller than in *n*-alkanes (2.545 Å) (22). As can be seen from the data given above, an analogous increase of the C—C bond length is also characteristic of cyclobutane, in which the distance between the non-bonded carbon atoms is only 2.04 Å.

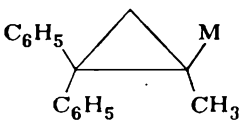
### 5.3.2. REACTIVITY

The specific properties of the cyclopropane ring are attributed, as has already been mentioned, to the unusual state of hybridization of its constituent carbon atoms and to the presence of banana bonds in the cyclopropane. The same factors exert a certain influence on the stereochemistry of substitution reactions in cyclopropane. Thus, the radical process of replacement of bromine by hydrogen (which usually involves racemization) in the case of optically active cyclopropyl bromides pro-

ceeds with retention of configuration, though it is accompanied by a considerable racemization (23):



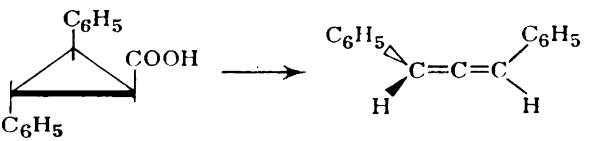

Practically completely racemized products are formed from optically active alkyl halides containing halogen at the asymmetric centre, usually in the course of organolithium or organomagnesium syntheses. On the contrary, retention of optical activity is observed in the corresponding syntheses in which use is made of organolithium and organomagnesium derivatives of cyclopropane. This has been established, for example, for compounds of the following type (24):



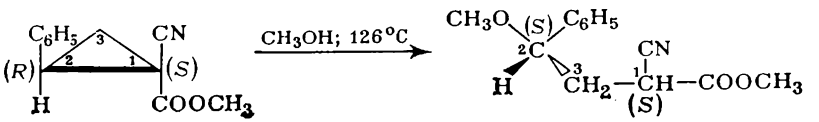

M = Li or MgX

In this connection, it is interesting to note that the tertiary cyclopropylalkyl cations have an increased conformational stability with a rotational barrier of about 59 kJ/mole (25).

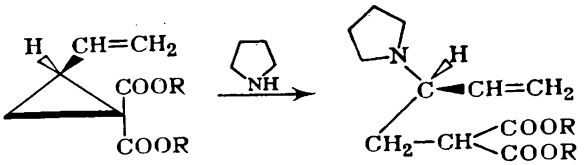
Optical activity is also retained in the conversion of cyclopropane compounds into allenes, say, of (—)-*trans*-2,3-diphenylcyclopropanecarboxylic acid into (+)-1,3-diphenyl-allene $\{[\alpha]_D^{24} = +797°$ (in alcohol)$\}$ (26):



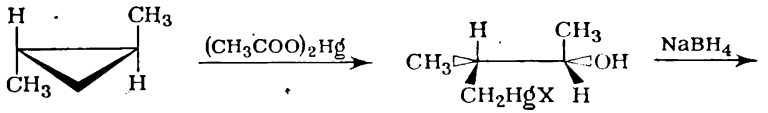

Optical activity is also retained in many other reactions involving the opening of the cyclopropane ring. Thus, for example, the addition of methanol proceeds with 100-percent inversion of configuration at C-2 (27):

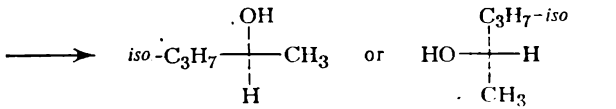


Other examples of the opening of the cyclopropane ring with retention of optical activity and inversion of configuration include the action of pyrrolidine on activated vinylcyclopropanes



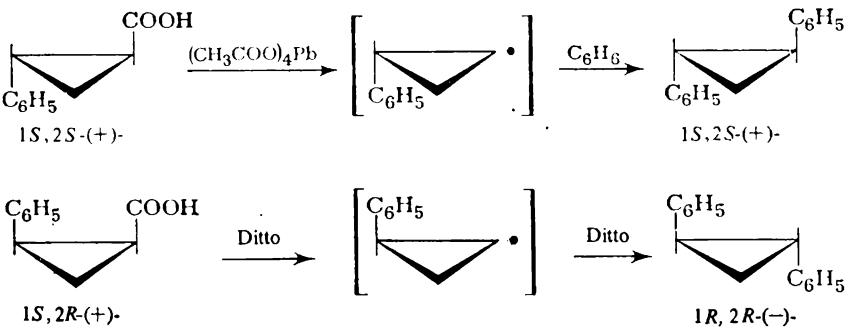
and the hydroxymercuration of *trans*-1,2-dimethylcyclopropane (28):





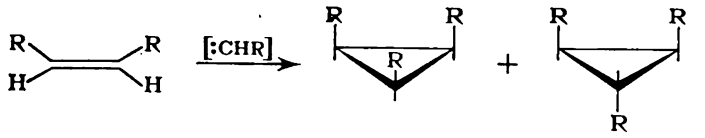
S-(+)-3-Methyl-2-butanol

The radical process of replacement of the carboxyl group of 2-phenylcyclopropanoic acid by a phenyl group is also highly stereospecific: the *cis*- and *trans*-isomers of the original acid, taken in optically active forms, are converted in this process into the optical antipodes of 1,2-diphenylcyclopropane (29):

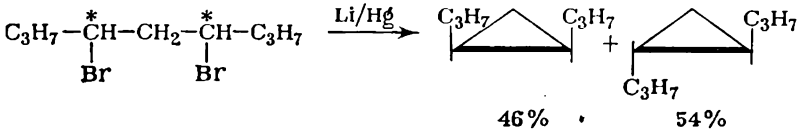


These results show that the phenylation of the transiently formed radical occurs at the *trans*-position to the phenyl group present in the molecule.

The more efficient path in the synthesis of trisubstituted cyclopropanes via carbenes under certain conditions has been found to be the one leading to the sterically more hindered stereoisomer (30):

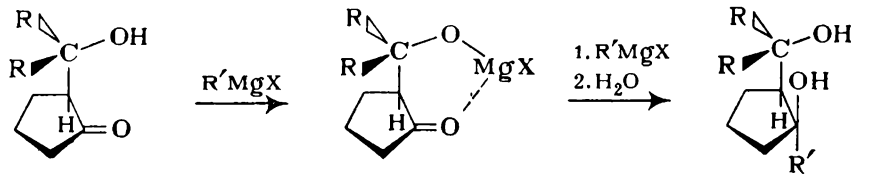



Optically active cyclopropanes are required as starting materials for many investigations. Apart from the usual resolution of racemic cyclopropane compounds into optical antipodes, another convenient method is suitable for their preparation—the cyclization of optically active 1,3-dihalides (31):




The optically active *trans*-form can be separated from the inactive *cis*-form by means of preparative-scale gas-liquid chromatography.

For ketones of the cyclopentane series there have been carried out detailed investigations of the stereodirectedness of reactions leading to the formation of the *cis-trans* isomeric forms of disubstituted cyclopentanes. Thus, the reduction of 2-alkylcyclopentanones effected by the action of lithium aluminium hydride and its trialkoxy analogues gave mixtures of the *cis-trans* isomeric 2-alkylcyclopentanols, the composition of which is quite close to the thermodynamically equilibrium composition (32). No high stereospecificity has been observed in the reactions of 2- and 3-alkylcyclopentanones with organomagnesium compounds either (33). A quite different result is observed in those cases when the substituent contains a hydroxyl group:



Owing to the replacement of the hydrogen of the OH group by the residue MgX and the formation of chelates, the radical approaches exclusively from the side opposite to the substituent, and the reaction becomes completely stereospecific (34).

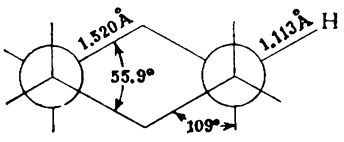
## 5.4. CYCLOHEXANE

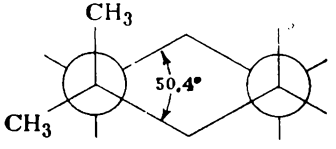
### 5.4.1. THE RING CONFORMATION

In 1890, Sachse advanced the assumption of the three-dimensional structure of alicyclic compounds. He pointed out, in particular, that two forms are possible for cyclohexane, the boat and chair conformations, which are free of angle strain.

Since the theory of strainless rings put forward by Sachse required the existence of two isomeric cyclohexanes and all attempts to find them failed, the views expressed by Sachse remained unrecognized for a long time. It was only in 1918 that the Sachse theory was revived by Mohr who explained the absence of isomeric cyclohexanes by the rapid interconversion of the two forms. Indeed, it is easy to accomplish such an interconversion on models, no considerable efforts being needed. At the same time, Mohr pointed out that the union of two cyclohexane rings may result in the formation of two sterically isomeric forms—the *cis*- and *trans*-decalins, which can no longer be interconverted without bond rupture. Later, these forms were really found (see page 379).

According to the original assumption, the boat and chair conformations were considered to be equally probable for cyclohexane. However, in 1947 Hassel established, by means of electron diffraction studies, that cyclohexane exists predominantly in the chair conformation. According to present-day electron diffraction data, cyclohexane (35) and 1,1-dimethylcyclohexane (36) have the following geometric parameters:

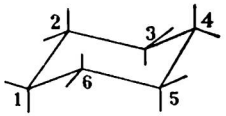


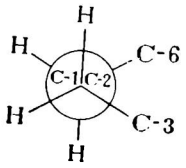




It is seen that the introduction of a *gem*-dimethyl grouping renders the cyclohexane ring more planar. On the schemes given above, the cyclohexane ring is pictured in the form of a double Newman projection which vividly demonstrates the steric relationships.

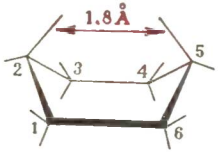
That the chair conformation is the preferred one can be deduced from general conformational considerations. In this form, the conformations

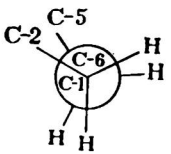
of the adjacent carbon atoms considered in pairs are of the staggered type:




Thus, the total conformational energy in the chair form of cyclohexane may be likened to the six-fold interaction in the skew conformation of butane. In the boat form, the spatial arrangement of two pairs of atoms at the bottom of the boat (C-1 and C-6; C-3 and C-4) correspond to the eclipsed conformation with an increased potential energy characteristic of this conformation.




Based on these considerations, one can calculate the difference between the internal energies of the boat and chair forms in the following manner:

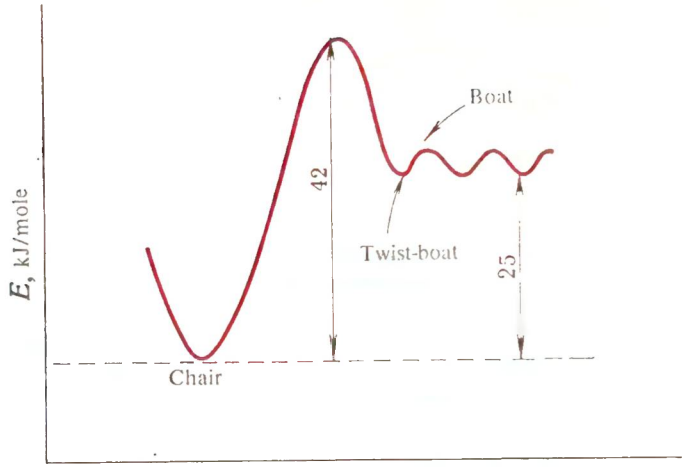
$$E_{\text{boat}} - E_{\text{chair}} = 2 \times 21 + 4 \times 3.4 - 6 \times 3.4 = 35 \text{ kJ/mole}$$

Here 21 kJ/mole is the approximate value of the energy of interaction of two methyl groups in the eclipsed ($\varphi^0$) conformation, and 3.4 kJ/mole is the energy of interaction of the same groups in the skew ($\varphi^1$) conformation.

Using a somewhat different method of calculation, Pitzer obtained a value of the order of 25 kJ/mole, and the value obtained by Barton by means of quantum-chemical calculations is 29 kJ/mole. The value ordinarily adopted ranges from 21 to 25 kJ/mole.

Apart from the factors mentioned above, there is one more factor by virtue of which the boat conformation is not the preferred one: the repulsion of the pair of hydrogen atoms that are at the top of the boat. The distance between their centres at normal tetrahedral angles should have been only 1.8 Å, while the sum of the van der Waals radii of the hydrogen atoms is 2.4 Å. This so-called bowsprit interaction too makes its contribution to the increased energy of the boat form.

Figure 5.2.



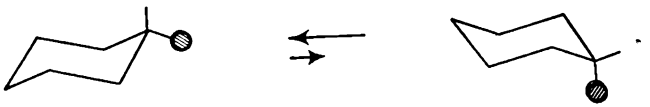

*The energetics of the conformational interconversions of cyclohexane.*

In considering the conformation of the cyclohexane ring one should also take into account the fact that the boat form is flexible. This enables it to assume the **twist-boat conformation,** which is energetically more favourable since there are no fully eclipsed conformations in it. The energetics of the interconversion of the various forms of cyclohexane are shown in Fig. 5.2. The potential barrier that separates the chair and boat forms from one another is equal to 42-46 kJ/mole according to NMR spectral data (the value 42 kJ/mole given in Fig. 5.2 has been determined by other methods). The energy difference between the chair and boat conformations is 21-25 kJ/mole; it means that there is one molecule in the flexible boat form per thousand molecules in the chair conformation (see Table 4.1 on page 226).

All the energy characteristics given above refer to the unsubstituted cyclohexane; the presence of substituents can change the energy relations between the conformations and even render the boat conformation more preferred in certain cases (see page 346).

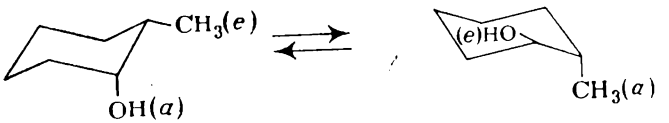
The inference as to the relative mobility of the boat form has so far been made on the basis of the corresponding models only. Of interest in this connection was the work of Kwart and coworkers (37), who claimed to have shown experimentally the greater mobility of the boat form by means of PMR spectroscopy. Unfortunately, two publications appeared later (38), which disputed the validity of the results obtained by Kwart and coworkers.

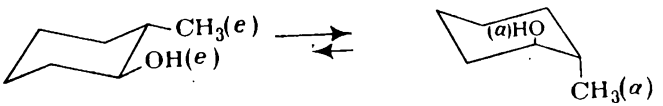
The cyclohexane ring has no absolute rigidity and can change its conformation. The "raised" carbon atoms are lowered and the "lowered" ones are raised; simultaneously, the axial bonds become equatorial and vice versa. Such a transformation is called an **interconversion.** In monosubstituted cyclohexanes, the interconversion proceeds to the side of formation of a conformer with an equatorially oriented substituent as the energetically more favourable one.



It is important to understand that this interconversion, just as the interconversions of disubstituted cyclohexanes considered below, involves no "rearrangement", i.e., the chemical bonds are neither broken nor reformed; only the conformation is changed. The NMR method allows such processes to be studied quantitatively. Thus, when the temperature decreases down to —110°C, it is possible to observe the separate signals of the equatorially and axially oriented methyl groups in the $^{13}$C-NMR spectrum of methylcyclohexane and to calculate the equilibrium constant (about 100) (39).

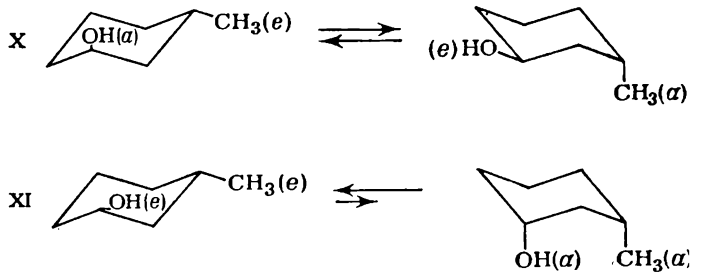
Depending on the orientation of the substituents, disubstituted cyclohexanes can be either equatorial-axial or diequatorial. Thus, for example, 2-methylcyclohexanol is known to have two stereoisomers, each of which can exist in two readily interconvertible conformations:

VIII 

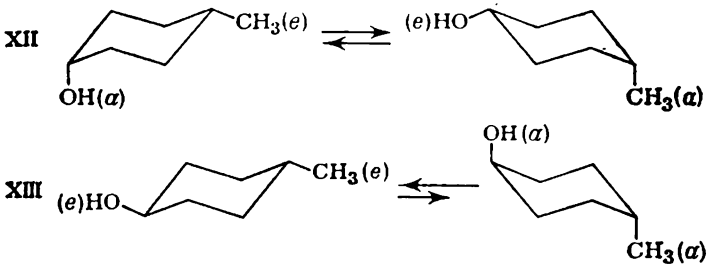

IX 


The diaxial conformation of stereoisomer IX is naturally energetically less favourable.

Two stereoisomers, each of which may assume two conformations, are also known to exist for 3-methylcyclohexanol:




4-Methylcyclohexanol also exhibits the same isomerism:

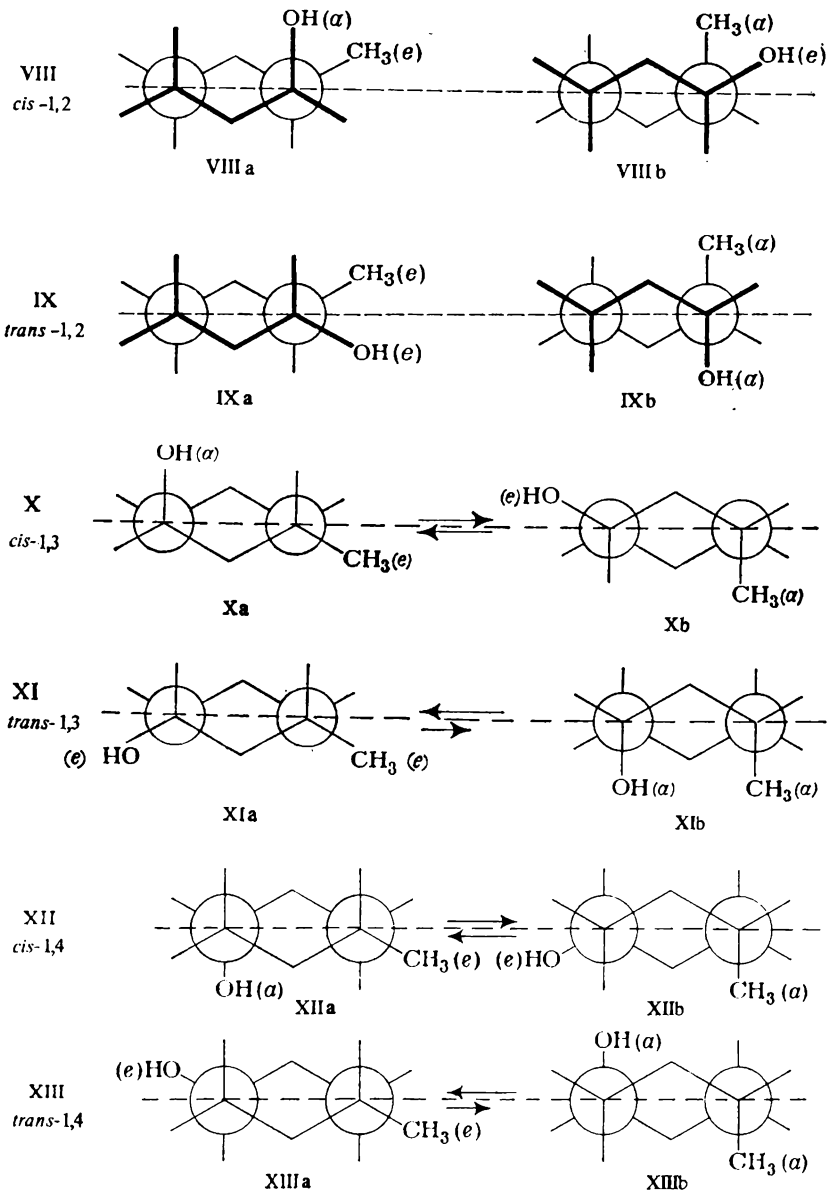



The existence of two geometric isomers for disubstituted cyclohexanes was known as early as the end of the last century. At that time the cyclohexane ring was considered to be planar, and the two isomers were believed to be the same *cis-trans* isomers as in small rings. The stereoisomeric 2-methylcyclohexanols were represented, for example, as follows:

As is clear from the foregoing, in fact there are no "true" *cis-* and *trans*-forms but these terms are still used at present. How are they related to the *ea-* and *ee*-arrangements of substituents considered above?

For more vividness, let us picture the cyclohexane molecule in a New-

man projection. The above-considered isomers VIII-XIII will look as follows in this projection:



The projections are conventionally separated by a horizontal dash line into the "upper" and "lower" parts. The stereoisomers in which both substituents are on the same side of this line are *cis*-isomers; those with the substituents being on the opposite sides of the central line are *trans*-isomers. True *trans* (IXb, XIIIb) and *cis* (XIb) arrangements are exhibited by three stereoisomers, IX, XI, and XIII, in unfavourable diaxial conformations. In the remaining conformations the angle between the bonds pointing towards the substituents is either 60° (VIIIa, VIIIb, IXa, XIIa, XIIb) or 120° (Xa, Xb, XIa).

Compounds VIII-XI completely lack elements of symmetry: therefore each of these stereoisomers is a racemate which can be resolved into a pair of optical antipodes. Compounds XII and XIII have a plane of symmetry passing through atoms 1 and 4; they cannot exist in optically active forms.

The possibility of optical antipodes being formed is reduced in the case of cyclohexanes with two *identical* substituents: only 1,2- and 1,3-*trans* isomers are asymmetric, whereas the *cis*-isomers are basically *meso*-forms which cannot be resolved because of internal compensation.

### 5.4.3. CONFORMATIONAL ENERGIES OF SUBSTITUENTS

As has already been mentioned, the equatorial conformation of substituents is more preferred than the axial conformation. The energy difference between molecules with a substituent in the axial and the equatorial conformation is called the **conformational energy.** This energy depends on the nature of the substituent. The greater the conformational energy the more liable is the corresponding substituent to occupy the axial position. The numerical values of conformational free energy $\Delta G$ are listed in Table 5.2. These data taken from a number of original works and from a book (40) allow us to make some interesting comparisons.

It is first of all obvious that the conformational energy is not dependent simply on the size of the substituent. Of decisive importance is the effective volume of the substituent — its size near the point of attachment to the cyclohexane ring. A comparison of the conformational energies of the hydroxyl group and its functional derivatives shows that, in spite of the substantial differences in the total volume of the substituent, the conformational energy remains practically constant. This happens because the "key" atom, i.e., the one directly attached to the cyclohexane ring, is the same in all cases: this is an oxygen atom.

The close conformational energies of the SH and $SC_6H_5$ groups again point to the primary importance of the effective volume of the substituent; as the effective volume of sulphur-containing substituents (S—H, SO—$C_6H_5$, $SO_2$—$C_6H_5$) increases their conformational energy increases also.

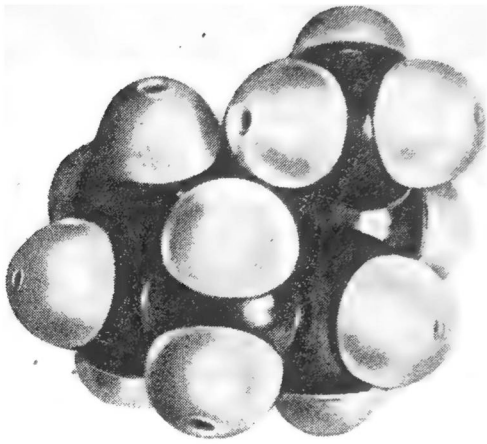
TABLE 5.2. THE CONFORMATIONAL FREE ENERGIES OF SUBSTITUENTS IN SUBSTITUTED CYCLOHEXANES

| Substituent | $\Delta G$, kJ/mole | Substituent | $\Delta G$, kJ/mole |
|---|---|---|---|
| $CH_3$ | 7.1 | COOH | 5.7 |
| $CF_3$ | 8.8 | $COOC_2H_5$ | 5.3 |
| $C_2H_5$ | 7.3 | $COO^-$ | 8.0 |
| *iso*-$C_3H_7$ | 9.0 | COCl | 5.2 |
| *tert*-$C_4H_9$ | 23.1 | N=C=O | 1.9 |
| $C_6H_5$ | 13.0 | $NO_2$ | 4.6 |
| C≡CH | 0.7 | $NH_2$, in an aprotic solvent | 5.0 |
| C≡N | 2.1 | in a protic solvent | 6.7 |
| F | 0.6 | $NHCOC_6H_5$ | 6.4 |
| Cl, Br, I | 1.7 | + | |
| OH, in an aprotic solvent | 2.2 | $NH_3$ | 8.0 |
| in a protic solvent | 3.7 | $N(CH_3)_2$ | 8.8 |
| O—CO—$CH_3$ | 2.5 | + | |
| O—$SO_2C_6H_4CH_3$-*p* | 2.1 | $N(CH_3)_3$ | 10.1 |
| O—$CH_3$ | 2.5 | SH | 3.8 |
| O—$C_2H_5$ | 3.8 | $SCH_3$ | 2.9 |
| | | $SC_6H_5$ | 3.4 |
| | | SO—$C_6H_5$ | 8.0 |
| | | $SO_2$—$C_6H_5$ | 10.5 |
| | | HgBr | 0 |

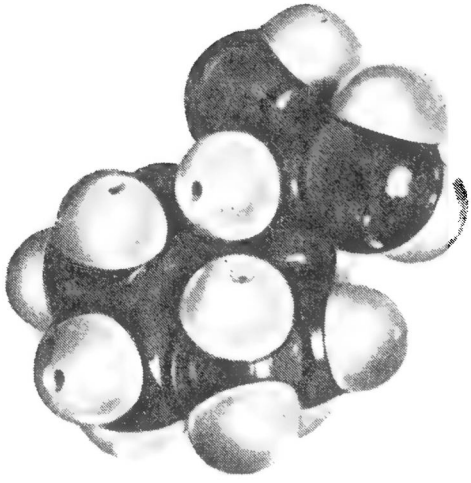
The effective volume of the substituent is not the only factor that determines its conformational energy. The electric charge also plays an important part. As shown by the comparison of the conformational energies of the carboxyl group and its derivatives, the negative charge considerably increases the conformational energy. This may be interpreted as a consequence of the increased repulsion between the anionic group and the electronic clouds of adjacent atoms. Evidently, for the same reasons the conformational energy of the $CF_3$ group with its enhanced electron density is higher than the conformational energy of the $CH_3$ group (the size of both groups is practically the same).

When considering the conformational energies of alkyl substituents, attention is drawn to the sharp jump of the conformational energy in going from the isopropyl to the *tert*-butyl radical. This is explained as follows. The increased energy of axial forms is mainly the result of non-bonded interactions between a substituent and axially oriented hydrogen atoms in the 1,3-positions. As a result of the rotation about

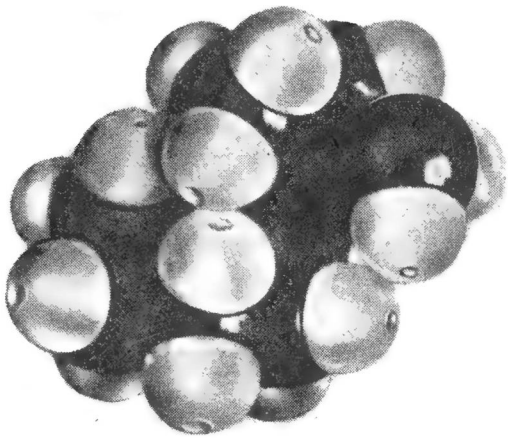
Figure 5.3.



a



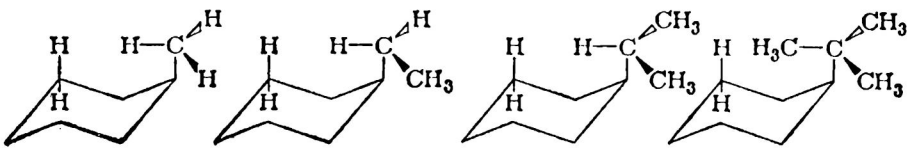
b



c

*Space-filling models of the axial forms of methylcyclohexane (a), isopropylcyclohexane (b) and tert-butylcyclohexane (c).*

the bond linking the isopropyl radical to the cyclohexane ring, it can adopt a conformation in which the hydrogen atom is directed into the ring. In this conformation, the 1,3-interaction of the isopropyl substituent differs little from the corresponding interaction between the $CH_3$ and $C_2H_5$ groups and, accordingly, their conformational energies are also only slightly different. The axial *tert*-butyl group cannot be turned in such a manner as to exclude the non-bonded interactions of one of its $CH_3$ groups with the axial hydrogen atoms in the 1,3-positions (Fig. 5.3); hence the increased conformational energy of this group.



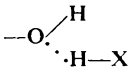
The high conformational energy of the *tert*-butyl group provides the fixing of conformations in which this group is equatorial. If there is a second substituent in the ring, it is thereby also fixed in a certain

conformation, equatorial or axial, depending on the position and configuration. This allows one to use such compounds for the investigation of the dependence of the properties of substituents on their equatorial or axial orientation (see page 338).

With decreasing temperature the rotation about the bond linking the *tert*-butyl group to the ring is also hindered (41); this is evidenced by the splitting of the signals in the PMR spectra, which is observed at temperature lower than —130°C.

In Table 5.2, the zero conformational energy of such a bulky group as HgBr draws attention. This is accounted for by the great length of the carbon-mercury bond and the easy polarizability of the mercury atom. A certain role is evidently also played by the reversed polarity of this bond with its $\delta^+$ charge on the mercury atom, whereas in most other cases the key atom carries a negative charge.

With many functional groups the conformational energy depends on the solvent used. It should be noted that the conformational energy of the OH group in protic solvent increases, which may probably be attributed to the formation of hydrogen bonds (H—X is the solvent molecule)



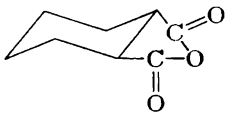
which leads to an increase of the effective volume of the substituent. A similar influence is exerted by protic solvents on the $NH_2$ group. A further example is the carbethoxy group, for which the conformational energy in isooctane is 4.36-4.48 kJ/mole, while in acetic acid it is 5.28 kJ/mole (42). These differences are believed to be associated with the formation of hydrogen bonds and also with the internal pressure of the solvent: the higher pressure favours the creation of a "more compact" conformation, i.e., the axial conformation.

Pentin (43) has carried out a detailed study of the conformational equilibrium of chloro- and bromocyclohexanes by means of IR and Raman spectroscopy. The conformational energy of the substituent for $C_6H_{11}Cl$ was found to be equal to $1.34 \pm 0.4$ kJ/mole in the gaseous state and to $1.18 \pm 0.4$ kJ/mole in the liquid state; the same conformational energy of the substituent was found for bromocyclohexane in the liquid state. The formation of two crystalline modifications was observed as the temperature decreased; one of them contained in its crystals both the equatorial and the axial form, and the other contained only the equatorial conformation. Thus, we are dealing here with a case of polymorphism, which is caused by the existence in crystals of different conformations.

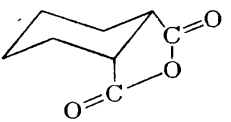
A review article devoted to the relation between the conformations of cycloalkyl halides $C_3$—$C_{10}$ and their IR spectra is available in the literature (44).

## 5.4.4. DI- AND POLYSUBSTITUTED CYCLOHEXANES

Complex cyclohexane derivatives containing several substituents tend to adopt, through interconversion, such a form in which the maximum possible number of substituents are found to be in the equatorial position. We have already dealt with the conformations of disubstituted cyclohexanes (see page 326). Let us emphasize once again that the concepts of *cis*- and *trans*-isomers are arbitrary in the case of cyclohexane derivatives. Instead of the dihedral angles between bonds, which are equal to zero (the *cis*-form) or to 180° (the *trans*-form), other angles are observed in the cyclohexane series and, accordingly, other distances between the substituents. For instance, in 1,2-disubstituted derivatives, in both configurations, the *cis*- and the *trans*-, the angle between the valence bonds is the same: it is only 60°, i.e., closer to the true *cis*-form. Therefore, for example, both stereoisomeric hexahydrophthalic acids are capable of forming cyclic intramolecular anhydrides (the orientation of the substituents is indicated):



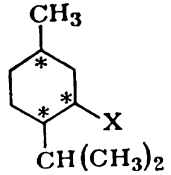
(*ee*)



(*ea*)

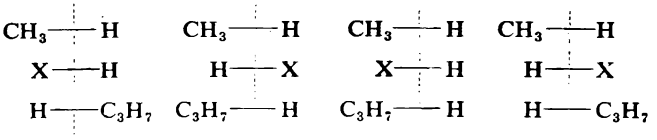
Taking into account the conformations of disubstituted cyclohexanes considered above, we can draw certain conclusions as to the stability of the *cis-trans* isomeric forms of such compounds. In pairs of isomeric 1,2- and 1,4-disubstituted derivatives of cyclohexane, the *trans*-isomer must be more stable since both substituents in it are oriented equatorially, whereas in their *cis* counterparts one of the substituents has an equatorial and the other an axial orientation. This conclusion is in full agreement with the conclusions made earlier on the basis of the classical conceptions, which do not take into account the non-planar structure of the cyclohexane ring. On the contrary, the inferences concerning the stability of the stereoisomers of 1,3-disubstituted cyclohexanes, which were made on the basis of the old and new conceptions, do not coincide. According to the present-day views, the *cis*-isomer must be more stable since in this case it is diequatorial. This is confirmed by experiment. It has long been known that the isomer of 1,3-dimethylcyclohexane, which is capable of existing in an optically active form (this may be only the *trans*-isomer by the condition of symmetry), is less stable than the other isomer, which is the *cis*-form. Analogous observations have been made for other 1,3-disubstituted cyclohexanes, such as 3-methylcyclohexanol, and 3-methylcyclohexylamine.

The classical examples of cyclohexane derivatives with *three* substituents are menthol and menthylamine:



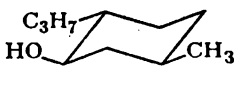

X = OH or $NH_2$

Having three non-identical asymmetric atoms, these compounds exist in eight stereoisomeric optically active forms which give rise to four pairs of racemates. The configurations of these compounds have been studied since the end of the last century in the works of Wallach. But neither Wallach nor Ried could in their earlier works tackle properly the problem of the configurations of the individual stereoisomers of menthol and menthylamine. This was done by Ried only in 1934 when the following configurations were elucidated:

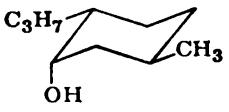



| $[\alpha]_D$ for | (−)- | (+)-*iso* | (+)-*neoiso* | (+)-*neo* |
|---|---|---|---|---|
| alcohols (X = OH) | −49.6° | +25.9° | +2.2° | +20.7° |
| amines (X = $NH_2$) | −44.56° | +28.96° | +2.32° | +15.12° |

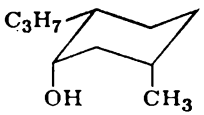
The configurations of four stereoisomers are conventionally represented above in the form of Fischer projection formulas; besides, they have four optical antipodes, which have mirror-image formulas and opposite signs of rotation. Based on these configurations, we can write the following most stable conformations for the same four compounds:



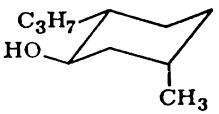

(−)-Menthol




(+)-Isomenthol



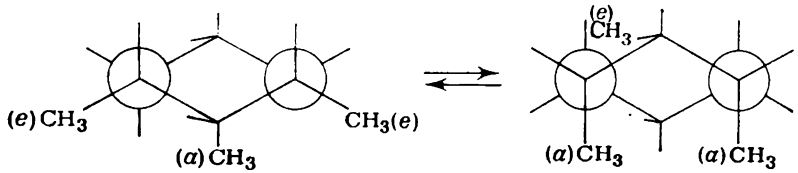

(+)-Neoisomenthol




(+)-Neomenthol

From the conformational schemes given it is seen that menthol (menthylamine) with all the three substituents being equatorial must be the most stable. The neoiso-forms in which two groups occupy the axial positions must be the least stable. This is what is actually observed in reality.

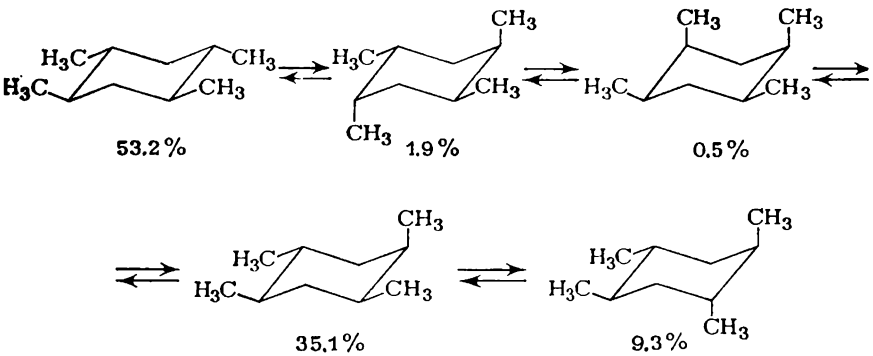
The conformational equilibrium between related compounds — four isomeric trimethylcyclohexanes — has been studied (45) by NMR spectroscopy using $^{13}C$; the results obtained were compared with the data calculated by the additive scheme. The essence of this scheme is demonstrated by the example of calculation for 1-*cis*-2-*cis*-3-trimethylcyclohexane which may exist in two interconvertible conformations:




XIVa XIVb

The form XIVa has two skew interactions of the $CH_3$ groups; in the form XIVb there is a 1,3-diaxial interaction in addition (its energy is 16 kJ/mole); hence, the conformation XIVa is energetically more favourable. The same conclusion has been drawn on the basis of NMR spectral data.

The specific conformational features of polymethylcyclohexanes containing up to six methyl groups have also been studied (46). At 300°C the following geometric isomers of 1,2,4,5-tetramethylcyclohexane are in thermodynamic equilibrium (we are dealing here with *isomers* and not with conformers!):

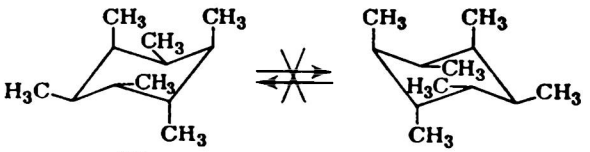


In full accord with the ordinary conformational concepts, the all-equatorial isomer is the most stable and therefore predominates in the thermodynamic equilibrium. As the number of axial substituents increases the population of the corresponding isomers in the thermodynamic equilibrium decreases.

Hexamethylcyclohexane having an all *cis*-configuration even at room temperature is completely locked in conformation XVa; for this conformation to be converted into conformation XVb, a potential barrier of about 70 kJ/mole must be overcome, though both conformations are basically identical—only the $CH_3$ groups in them exchange their roles:

XVa XVb

The authors of the work under discussion point out that if such a high barrier to interconversion is displayed by the other isomer, its resolution into optical antipodes can be predicted since the forms XVb and XVd are chiral in this case:

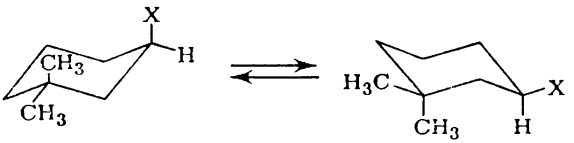


XVc XVd

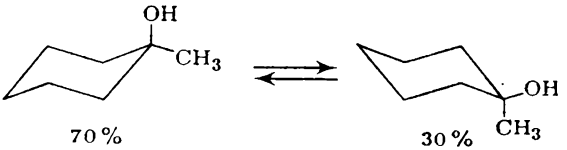
The conformational energies in substituted derivatives of cyclohexane may differ significantly from the corresponding energies for the unsubstituted ring. Thus, the conformational energies $\Delta G$ of the halogen atoms and the hydroxyl group in *gem*-dimethylcyclohexanes are as follows (in kJ/mole) (47):

| Substituent | For cyclohexane | For 4,4-dimethyl-cyclohexane | For 3,3-dimethyl-cyclohexane |
|---|---|---|---|
| Fluorine | 1.13 | 0.76 | 2.69 |
| Chlorine | 2.31 | 1.80 | 6.29 |
| Bromine | 2.01 | 2.01 | 6.29 |
| Iodine | 1.96 | 1.80 | 6.29 |
| Hydroxyl | 3.91 | 3.78 | 6.29 |

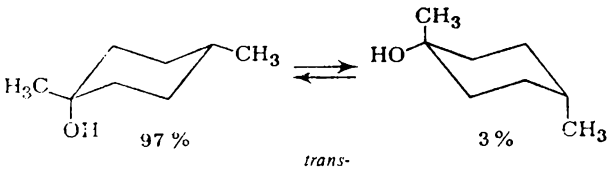
The sharp increase of conformational energy for 3,3-*gem*-dimethyl derivatives is associated with the additional destabilization of the axial conformations due to the *syn*-1,3-axial interaction between the methyl group and the substituent:

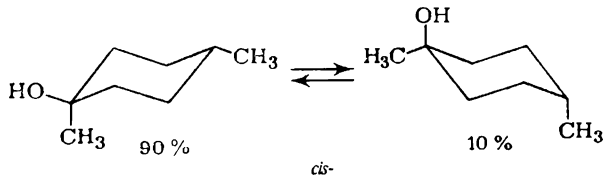



In cyclohexane derivatives that have two different substituents, the substituent with a lower conformational energy is forced into the axial position if necessary. Thus, of the two conformations of 1-methylcyclohexanol the one in which the $CH_3$ group (with a higher conformational energy) is equatorial predominates:



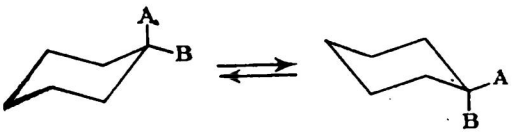

The free energy of this conformational equilibrium in a solution of dimethyl sulphoxide at 35°C is equal to 1.5 kJ/mole. With *cis-trans* isomeric 1,4-dimethylcyclohexanols the conformational equilibrium corresponds to the following contents of the conformers:




After the numerical values of conformational energy of the substituents in the cyclohexane ring had been found, the question that natu-

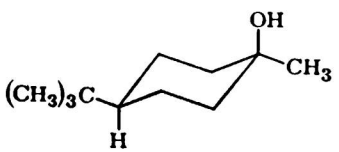
rally faced the investigators was the question of the *additivity* (or non-additivity) of these energies in the presence of several substituents. In one of the works devoted to this problem (48), the conformational energy of 1,1-disubstituted cyclohexanes was calculated as the difference between the conformational energies of the corresponding groups and was also determined experimentally (by means of NMR spectroscopy) from the position of the conformational equilibrium:



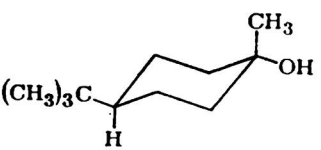

The two values were found to be in good agreement:

| A | B | Difference between conformational energies of groups, kJ/mole | Experimental conformational energy, kJ/mole |
|---|---|---|---|
| $CH_3$ | Cl | 5.5 | 4.6 |
| $CH_3$ | CHO | 1.5 | 0.6 |
| $C_6H_5$ | $N(CH_3)_2$ | 4.2 | 2.1 |
| $C_6H_5$ | $\overset{+}{H}N(CH_3)_2$ | 2.9 | 0.8 |
| OH | C≡CH | 1.7 | 2.5 |

In another work (49) it was pointed out, on the contrary, that there is no additivity of conformational energies for 1-methyl-4-*tert*-butylcyclohexanol taken as an example. Because of the presence of the *tert*-butyl group with its high conformational energy, a conformation with an equatorial *tert*-butyl group is fixed in both isomers of this compound:




*trans-*

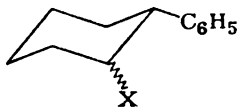



*cis-*

The conformational free energy $\Delta G$ can be calculated as the difference between the conformational energies of the $CH_3$ and OH groups:

it is equal to about 5 kJ/mole, the experimental value being 1.01 ± 0.04 kJ/mole.

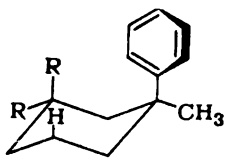
The PMR and IR spectroscopy and also the method of circular dichroism have been used for a detailed study of phenylcyclohexanes with different substituents in position 2. These compounds exist exclusively in a conformation with an equatorial phenyl group (50), which, like the *tert*-butyl group, is also capable of fixing the conformation:



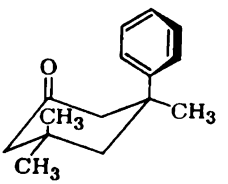

X=OH, $NH_2$, $CH_2OH$, COOH, $COCl_3$

For the sign of the Cotton effect characteristic of these compounds to be determined, a rule has been suggested, which relates the configuration to the sign of the circular dichroism band.

The conformation with an equatorial phenyl group has also been confirmed for phenylcyclohexane by means of calculations (51). This is not surprising in view of the considerable conformational energy of the phenyl group. Surprising is the fact that in compounds XVI and XVII shown below the phenyl group is *axial*; for the 1,3-interaction to be decreased, the phenyl group is turned perpendicularly to the plane of the drawing:




XVI

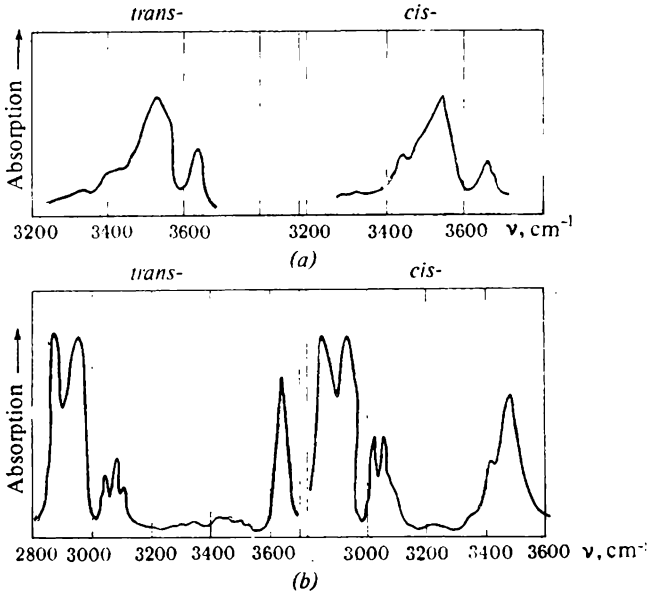



XVII

The conformation with an axial phenyl group is found to be fixed in compound XVII according to NMR spectral data also (52).

2-Aminocyclohexanols may serve as examples of compounds, the conformational characteristics of which depend, to a considerable extent, on the intramolecular hydrogen bond (53). In the IR spectra of such compounds the absorption band of the hydroxyl group (3600 $cm^{-1}$, the "free" hydroxyl group) is shifted to lower frequencies in the case of formation of hydrogen bonds. The magnitude of this shift and the intensity of the corresponding band may serve as a measure of the "bondedness" of the hydroxyl.

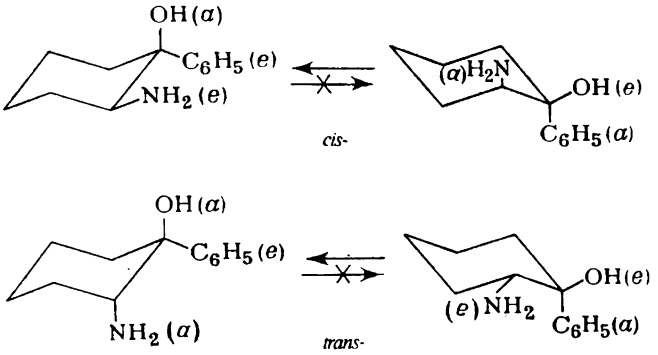
Figure 5.4.




*The IR spectra of the isomers of* 2-*aminocyclohexanol (a) and* 1-*phenyl*-2-*aminocyclohexanol (b).*

If the IR spectra of the *cis*- and *trans*-forms of 2-aminocyclohexanol given in Fig. 5.4 are compared, it will be seen that the difference between the spectra of the isomers is insignificant: the spectra of both isomers contain a band corresponding to the bound hydroxyl group and a band (weaker) of the free OH group. Hence, in the *trans*- as well as the *cis*-form the hydroxyl and amino groups interact with each other to form a hydrogen bond. Such a result is in full agreement with the conception of the chair conformation of the cyclohexane ring, in which, as has already been mentioned, the distance between the 1,2-substituents is the same in both stereoisomers, i.e., the *cis*- and *trans*-forms. The introduction of a bulky substituent at the carbon atom bearing a hydroxyl group changes the situation substantially. With 1-phenyl-2-aminocyclohexanol the formation of a hydrogen bond is possible only in the case of the *cis*-isomer. This is because the introduction of a phenyl radical fixes the conformation with an

equatorial phenyl group and the possibility of an interconversion is excluded:



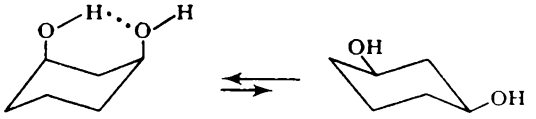

In the *cis*-form, the hydroxyl group is arranged axially and the amino group equatorially; with the dihedral angle between them being equal to 60° an intramolecular hydrogen bond may be formed, and therefore the IR spectrum of the *cis*-isomer contains no band of the free hydroxyl group. The *trans*-isomer is also fixed in the conformation with an equatorial phenyl group, but the hydroxyl and amino groups occupy here the axial position, the dihedral angle between them is 180° and the formation of an intramolecular hydrogen bond is impossible.

If the formation of intramolecular hydrogen bonds is to be proved by means of IR spectroscopy, the IR spectra must be taken at different concentrations, including large dilutions, since only the fact that the position and the intensity of the absorption band of the bound hydroxyl group are independent of the concentration may serve as a proof of the formation of an intramolecular hydrogen bond. But if on dilution there occur substantial changes, this is evidence of intermolecular association via hydrogen bonds.

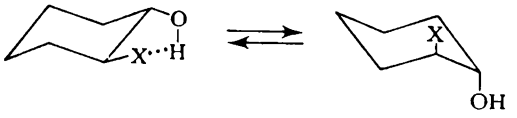
In the investigation under consideration, just as in other analogous studies, it is assumed that the conditions for the formation of a hydrogen bond in α-glycols, 1,2-aminohydroxy compounds and other similar compounds are most favourable at zero dihedral angle of O—C—C—O (accordingly, of O—C—C—N). It is believed that the smaller this angle the stronger the hydrogen bond and, hence, the stronger is the shift of the band in the IR spectrum. It has however been shown recently (54), for diols of the norbornane series, bicyclo[2.2.2]octane and adamantane, that vicinal diols with zero dihedral angle may also have an unusually weak hydrogen bond, i.e., the direct relation between the shift of the OH band and the dihedral angle was found to be dubious.

The preference of the equatorial conformation, which has undoubtedly been observed in many cases, is not indisputable either. For instance, for dihalogenocyclohexanes the diaxial form is energetically more favourable in a number of cases. Thus, in *trans*-1,2-dibromocyclohexane in the liquid state the energy of the diequatorial form is 1.4 kJ/mole higher than the energy of the diaxial form; this is responsible for the fact that the population of the diequatorial form in the conformational equilibrium is only 35 per cent. In the gaseous state the fraction of this conformation falls to 5 per cent, and in a solution of carbon tetrachloride it is 16 per cent (55). These data originally obtained by optical methods (IR and Raman spectroscopy) are also supported by the NMR data (56).

*trans*-1,2-Dichlorocyclohexane in crystals exists only in the *ee*-conformation; in the liquid state a certain amount of the diaxial form appears, and in the gaseous state the diaxial form predominates (57). The diaxial form stabilized by a hydrogen bond also predominates in *cis*-cyclohexane-1,3-diol:

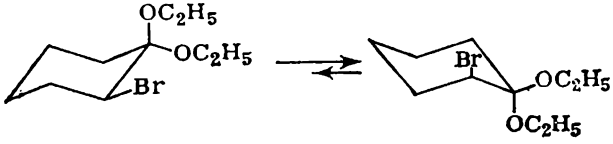



In *cis*-4-bromo-1-methylcyclohexane and *cis*-4-chloro-1-bromocyclohexane the bromine atom is in the axial position in spite of its greater mass and volume as compared with the methyl group or the chlorine atom. Very small differences between the conformational energies have been found for the *ee*- and *aa*-conformers of *trans*-2-halogenocyclohexanols (58):

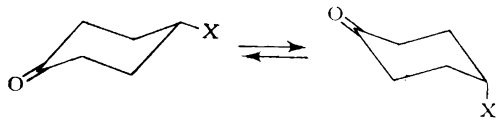



Despite the presence of an intramolecular hydrogen bond in the *ee*-conformation, the dipole-dipole repulsion lowers its stability. With *trans*-2-bromocyclohexanol the value of $\Delta H^0$ is —8.80 kJ/mole (in a solution of carbon tetrachloride).

Because of the dipole-dipole repulsion the equatorial conformation of the diethyl ketal of 2-bromocyclohexanone is also destabilized (59):



The data obtained in the study of the conformation of 4-substituted cyclohexanones have been found to be conflicting. While the analysis of the dipole moments showed that the equatorial conformation was the preferred one, more recent NMR spectral data indicate the preferableness of the axial conformation (60):




The population of the axial conformation with different X is as follows (in benzene solutions, in per cent):

| OH | $OCOC_6H_5$ | Cl | Br | I | $OCH_3$ |
|---|---|---|---|---|---|
| 53 | 60 | 60 | 54 | 55 | 73 |

2-Bromocyclohexanone may, in principle, exist in two conformations, with an equatorial or axial bromine atom:

The general conformational rules point to the preference of the equatorial conformation. The conformational energy of bromine, however, is not high (about 1.7 kJ/mole, see Table 5.2); besides, in this particular compound the equatorial conformation is destabilized by the unfavourable parallel arrangement of the dipoles of the C=O and C—Br bonds. As a result of this, apart from the equatorial form, a considerable amount of the axial form is also present. The population of the axial form depends on the nature of the solvent and the concentration and may amount up to 50 per cent.

Analogous observations have been made for other compounds as well. Thus, *trans*-2-chloro-5-methylcyclohexanone has the diequatorial conformation in a polar solvent, say methanol, but in a non-polar solvent (octane) it adopts the diaxial conformation. This phenomenon was discovered by Allinger and Djerassi in 1958, who studied the optical rotatory dispersion of the compound in question: the ORD curves have different signs of the Cotton effect in methanol and octane (Fig. 5.5).

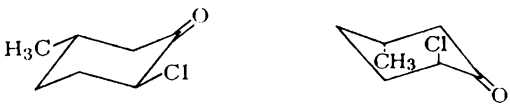
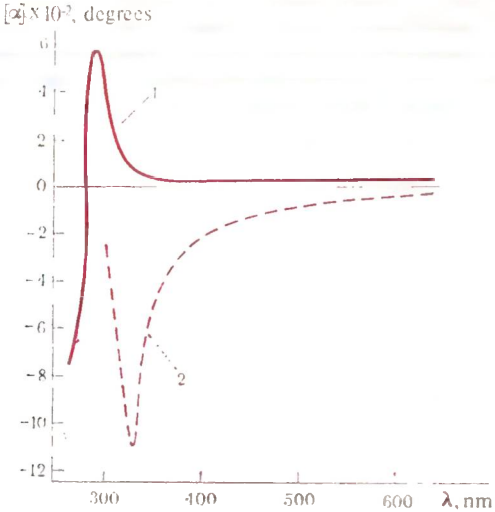


Figure 5.5.




*The optical rotatory dispersion curves of trans-2-chloro-5-methylcyclohexanone in methanol (curve 1) and in octane (curve 2).*

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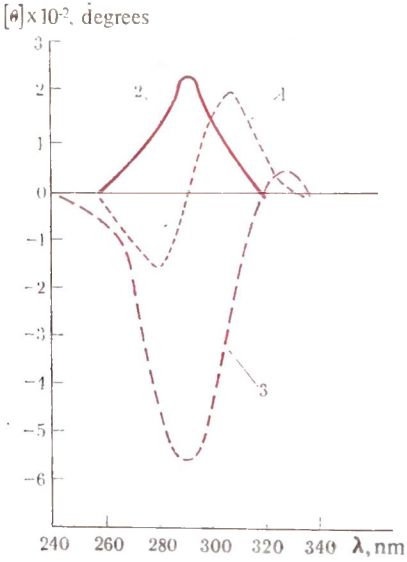
Figure 5.6.

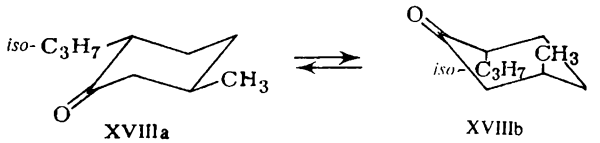



*The circular dichroism curves of menthone in methanol (curve 1), in water (curve 2) and in isooctane (curve 3).*

---

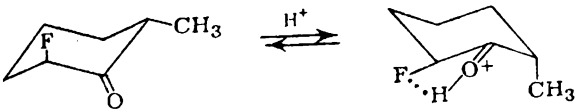
That the conformation varies, depending on the nature of the solvent, has also been established in the spectropolarimetric investigations of 2-hydroxycyclohexanones (61) and 2-alkylcyclohexanones (62). Especially interesting is the latter case where we are dealing with the violation of the rule of equatorial preference not for such substituents as the halogen atom or the hydroxy group (which may be caused by the dipole-dipole repulsion between the C=O group and the halogen atom or, respectively, the hydroxy group) but for simple alkyl substituents.

The CD curves (just as the ORD curves) of menthone are dependent on the nature of the solvent (Fig. 5.6). The optically active band of the carbonyl group gives a negative CD band in menthone dissolved in a non-polar solvent (isooctane); in aqueous solution this band becomes positive (in spite of the low solubility of menthone in water, a concentration can still be produced, which is sufficient for measurements). This may be attributed to conformational interconversions; with account taken of the octant rule it may be assumed that the diequatorial conformer XVIIIa predominates in polar media and the conformer XVIIIb with the diaxial orientation of both alkyl groups in non-polar media:

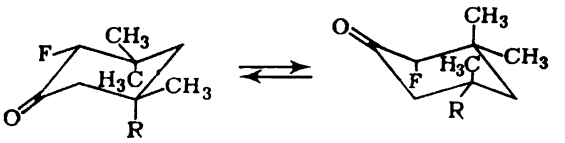



XVIIIa XVIIIb

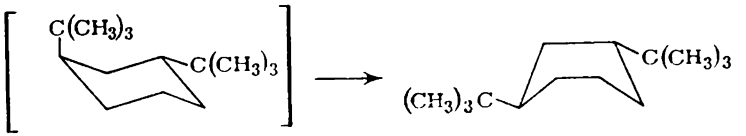
Under the action of "superstrong" acids 2-halogenocyclohexanones undergo protonation at the carbonyl group, which leads to the formation of a hydrogen bond to the adjacent halogen atom and to the corresponding change of the conformation (63):



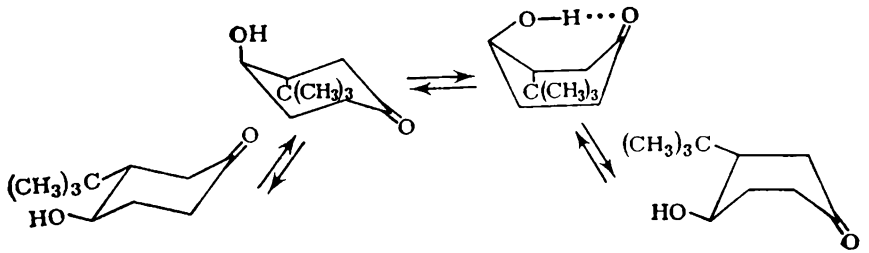

With polysubstituted cyclohexanones there have also been observed the coexistence of two conformers, the conformation with an axial fluorine atom predominating in polar solvents (64):



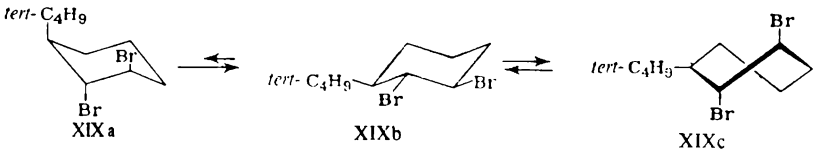
We have so far dealt with compounds in which the cyclohexane ring has a chair form. In certain cases, however, the boat form (or the twist-boat form) may also appear to be more stable. Thus, for example, in the case of *trans*-1,3-di-*tert*-butylcyclohexane in the chair conformation, one of the *tert*-butyl groups should have been in the axial position, which would have increased the energy of the molecule by about 25 kJ/mole. Having flipped to the boat form, this molecule may adopt a more preferred conformation with equatorial *tert*-butyl groups (65):




Several conformations, including the boat conformation, have been established for 4-hydroxy-3-*tert*-butylcyclohexanone (66):




In the conformational equilibrium of *r*1,*t*2-dibromo-*c*3-*tert*-butylcyclohexane (for the notation, see page 314) there is the twist-boat form present (XIXc) since the chair conformation XIXb is destabilized due to the interaction of the *tert*-butyl group with the bromine atom and also to the dipole-dipole repulsion of the bromine atoms. The form XIXa is not the preferred one because of the presence of three axial substituents (67):



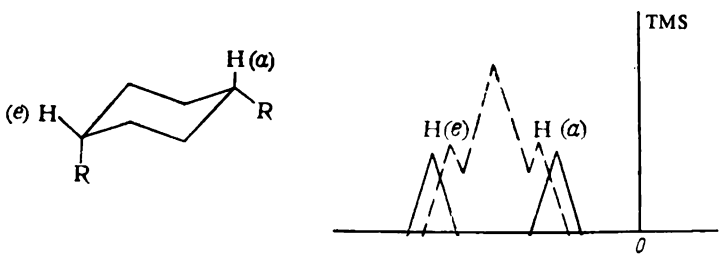

The mutual effect of the substituents in the cyclohexane ring is also manifested in the form of the so-called reflex effect (68). It consists

in that two axial substituents in the 1,3-positions not only destabilize the third axial substituent on the same side of the ring in position 5 (due to the diaxial interaction) but also exert an influence on the axial substituents on the opposite side of the ring (in positions 2, 4, 6), bending them towards one another and increasing the conformational energy.

Substituents that have no cylindrical symmetry may not only be axial or equatorial but may have one more conformation at the bond linking them to the cyclohexane ring. As an example may be cited the carboxyl group (69). In conclusion, the reader is referred to review articles (70) dealing with the problems of conformational analysis discussed in this section.

### 5.4.5. ISOLATION OF INDIVIDUAL CONFORMERS

Conformers (rotational isomers) are, by definition, the geometrical forms of molecules, which cannot be isolated in the free state. With the advancement of science it however becomes obvious that under certain conditions there can be obtained "pure" individual conformers. The relevant information has been obtained with the aid of nuclear magnetic resonance spectroscopy (see ref. 71). The use of this method for the conformational studies of cyclohexane compounds is based on the fact that methine axial and equatorial protons give signals with different chemical shifts in NMR spectra:



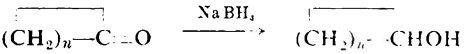

In rigid cyclohexane systems there can be observed two separate signals. In mobile systems in which the cyclohexane ring rapidly changes its form as the result of interconversion, both signals merge into a complex multiplet. If such a compound with the mobile cyclohexane ring is cooled, there will come a moment when the multiplet is split into the signals of protons H(*a*) and H(*e*). This means that at the given temperature the interconversion is stopped and the compound is frozen in the form of a pure conformer (or a mixture of conformers). The areas of the H(*a*) and H(*e*) signals will indicate the ratio of conformers.

The application of this method to chlorocyclohexane has shown that at —150°C from a solution in deuterated vinyl chloride there is crystallized a pure equatorial conformer which survives at this temperature for several hours (72). In an analogous way, there has been detected, with the aid of $^{13}$C-NMR, the equatorial conformer of methylcyclohexane, which is in equilibrium with the axial conformer in the proportion of about 100 : 1. This enables the conformational energy of the methyl group to be calculated: the value found (6.6 kJ/mole) is in good agreement with the usually accepted value.

### 5.4.6. REACTIVITY OF CYCLOHEXANE DERIVATIVES

Compounds with the equatorial and axial orientation of substituents differ not only in physical properties but in reactivity as well. The rates of formation of equatorial and axial isomers and the rates of elimination and substitution reactions involving such compounds are also different.

The specific reactivity of cyclic systems was explained by Brown at the beginning of the fifties, who suggested the concept of *I* strain (internal strain). The essence of this concept is simple: those reactions proceed readily, in which the *I* strain in the transition state and in the final product is lower than in the starting material. Changes in the *I* strain were attributed by Brown primarily to changes in the state of hybridization of the carbon atom during the course of the reaction. Thus, in the reduction of ketones the trigonal $sp^2$-hybridized carbon atom turns into a tetrahedral carbon atom. Depending on the nature of a ketone, this reaction




proceeds at different rates:

| | Relative rate |
|---|---|
| Aliphatic ketones | 1 |
| Cyclobutanone | 581 |
| Cyclopentanone | 15.4 |
| Cyclohexanone | 355 |
| Cycloheptanone | 2.25 |
| Cycloheptadecanone | 1.31 |

The rate of reduction of cyclobutanone is high since the reaction is accompanied by a considerable decrease of the angle strain. Using

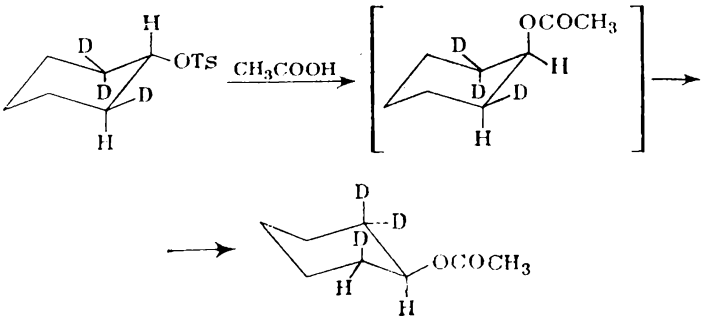
the formula given on page 308, one can make the following calculation:

$$\Delta E_1 = 0.084\,(120 - 90)^2 - 0.084\,(109.5 - 90)^2 \approx 43 \text{ kJ/mole}$$

A slight increase of the eclipsing strain does not affect the general preference of the reduction process.

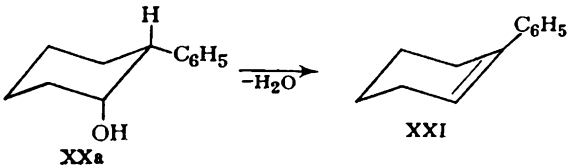
In the reduction of cyclopentanone, the angle strain (calculated in the same manner) increases by about 7 kJ/mole, the eclipsing strain also increases and, accordingly, the rate of the reaction falls. The internal CCC angle (about 100°) in cyclohexanone and cyclohexane corresponds to the state of $sp^3$-hybridization and therefore the conversion during the course of reduction of cyclohexanone again proceeds rapidly. There is no eclipsing strain in the cyclohexane chair which consists entirely of skew conformation segments.

The *I*-strain concept has been successfully used in other cases as well (see ref. 73). It should be emphasized at the same time that conformations and their energies can now be estimated much more precisely than it was done by Brown 25 years ago, and the concept of *I* strain is of no great importance as a general principle. The low conformational mobility of cyclohexane and its derivatives as compared with compounds of the aliphatic series is responsible for the more pronounced manifestation of steric factors in reactions of cyclic compounds. Thus, using deuterium as a label, it has been established that the reaction of solvolysis of cyclohexyl tosylate proceeds with inversion of configuration followed by the conversion into a more stable conformation (74):

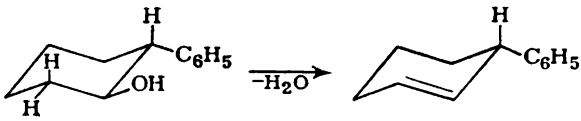



In the series of cyclohexane derivatives, it is easy to observe the manifestation of the rule of transoid elimination in *E*2-type reactions. When the elements of water are eliminated from stereoisomeric 1-phenyl-2-cyclohexanols (fixed only in the conformation with an equatorial phenyl group due to the high conformational energy of the phenyl group), only the *cis*-isomer XXa with a hydrogen atom at a tertiary carbon

atom in the transoid position to the hydroxyl group loses the elements of water under the action of phosphoric acid to form 1-phenylcyclohexene XXI. The *trans*-form XXb gives the other isomer (which differs by the position of the double bond), 3-phenylcyclohexene XXII (110):



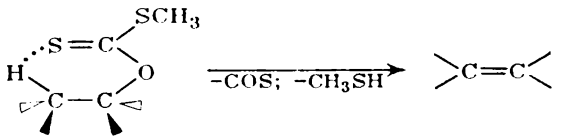

XXa XXI



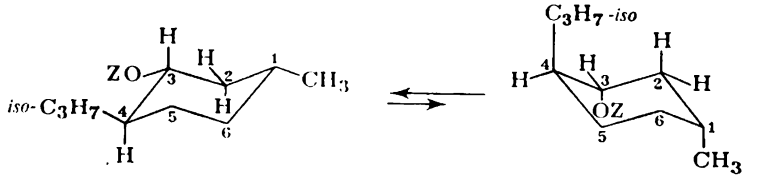

XXb XXII

1-Phenylcyclohexene XXI cannot be formed from compound XXb because the starting compound contains, at C-1, no hydrogen atom occupying the transoid position to the hydroxyl required for the elimination.

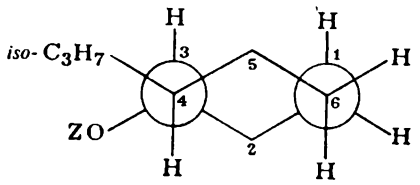
There are reactions that proceed by the scheme of *cis*-elimination. In this case, the reaction evidently proceeds via a cyclic transition state with the formation of a bond between the two leaving groups, say, the hydrogen atom and the xanthate residue in the Chugaev reaction:



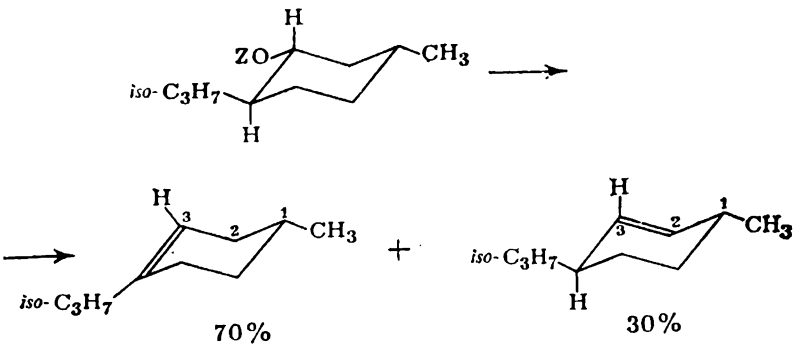

An example of such elimination reactions is the preparation of olefins from the xanthates of stereoisomeric menthols. Menthyl xanthate in its stable conformation has three substituents which are in the equatorial position; the inverted form with three axial substituents is quite unfavourable (Z stands for the —CS—$SCH_3$ residue):



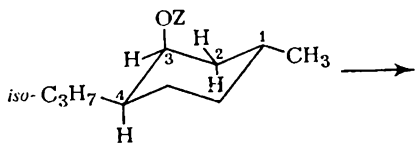
The cyclic transition state required for the Chugaev reaction to be effected can be formed in the stable triequatorial conformation of menthyl xanthate due either to the hydrogen atoms at C-2 or to the hydrogen atom at C-4, the latter being preferred in accordance with Zaitsev's rule (the elimination of hydrogen from the least hydrogenated carbon atom). The possibility of a cyclic transition state being formed between the equatorial group OZ and the axial hydrogen at C-4 is clearly seen when cyclohexane is represented in a Newman projection:

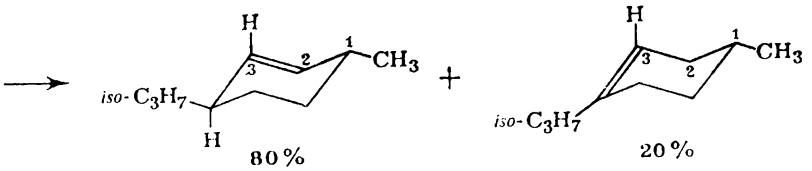



Thus, in menthyl xanthate, the Zaitsev elimination is not hindered at all and the major product of this reaction is 3-menthene and the minor product (due to the hydrogen at C-2, in contrary to Zaitsev's rule) is 2-menthene:




Another diastereomer, neomenthyl xanthate, has, in its stable conformation, a hydroxyl group in the axial position. The hydrogen at C-4 is also axial and occupies the transoid position relative to the hydroxyl group, and the cyclic transition state of the type indicated cannot be formed. It may appear due only to the equatorial hydrogen at C-2 and the major product is therefore 2-menthene:






The difference in reactivity between equatorially and axially oriented functional groups may also be illustrated by the fact that, for example, the axial hydroxyl group in the series of cyclohexane derivatives undergoes acylation more slowly than the equatorial one, and the resulting axial ester, in addition, is hydrolysed more slowly. It is believed that on acylation or hydrolysis the reaction proceeds in the conformation with an equatorial hydroxyl group; if it is axial in the starting compound, it must first be converted into the equatorial form. According to these conceptions, the relative rates of the acylation of isomeric menthols must decrease in the following sequence: menthol, isomenthol, neoisomenthol, neomenthol; this is confirmed by experiment.

The axial methyl group next to the equatorial carbomethoxy group, $COOCH_3$, slows down the hydrolysis of the latter less strongly than does the adjacent equatorial $CH_3$ group (75). With the axial orientation of the carbomethoxy group the effect of the adjacent axial or equatorial methyl group is reversed: it is now the equatorial $CH_3$ group which slows down the hydrolysis less strongly.

The axial alcohols in the cyclohexane series are more readily oxidized to the corresponding ketones than the equatorial alcohols; it is believed that the action of the oxidizing agent (in particular, chromic anhydride) is directed to the hydrogen atom at a carbon atom bearing a hydroxyl group: if the OH group is axial, this hydrogen atom is equatorial and is in this form more accessible to the oxidizing agent.

Especially pronounced are the differences in reactivity between rigid rings where the spatial orientation is completely fixed. The discussion of this subject will therefore be continued in the section devoted to condensed-ring (fused-ring) structures.

### 5.4.7. REDUCTION OF KETONES OF THE CYCLOHEXANE SERIES

In 1953 Barton (76) put forward the following ideas concerning the steric occurrence of the reduction of alkylcyclohexanones on the basis of conformational conceptions:

1. The catalytic hydrogenation in acid medium gives predominantly an axial alcohol.

2. In the catalytic hydrogenation in neutral medium (which proceeds more slowly) an axial alcohol is mainly formed from sterically

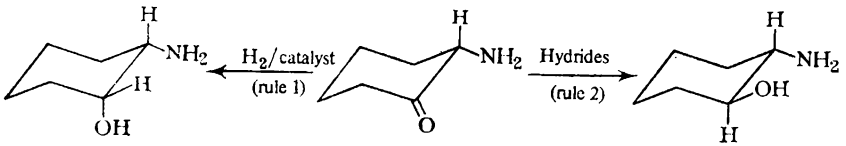
hindered ketones (see below) and an equatorial alcohol from sterically unhindered ketones.

3. The reduction with aluminium isopropylate gives a larger amount of an axial alcohol than the reduction effected by other methods (sterically hindered ketones are not reduced by this method).

4. The reduction with lithium aluminium hydride proceeds in accordance with rule 2.

5. When the reduction is effected with sodium, an equatorial isomer is predominantly formed in the alcohol; the composition of the mixture obtained corresponds to the position of the thermodynamic equilibrium.

The sterically hindered ketones that are meant here are those in which, because of the presence of substituents near the carbonyl group, the reactivity of the carbonyl group is reduced. It should be pointed out here that no sharp boundary line can be drawn between sterically hindered and unhindered ketones. An example is the reduction of 2-aminocyclohexanone (77):




When subjected to hydride reduction this ketone thus behaves as a sterically unhindered one, in spite of the presence of a substituent near the carbonyl group.

Of the rules proposed by Barton only rules 1 and 5 were fully confirmed by detailed studies carried out, for example, by Hückel; as regards the reductions with hydrides and aluminium isopropylate the situation proved to be much more complicated.

The reduction of the carbonyl group with hydride reagents is in general the more stereospecific the larger is the volume of the reducing agent. It has however been noted that $LiAlH(OC_4H_9\text{-}tert)_3$ provides lower stereoselectivity than the less bulky $LiAlH(OCH_3)_3$ (78). The seeming contradiction was clarified when account was taken of the degree of association of the corresponding reagents in solutions: their true "volumes" are arranged in the following order:

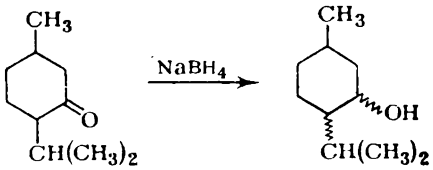
$$LiAlH(OC_4H_9\text{-}tert)_3 < LiAlH_4 < LiAlH(OCH_3)_3$$

because of the *tert*-butyl reagent being completely unassociated. It was also pointed out in the work under consideration that in the reduction of 2-methylcyclohexanone by the action of $LiAlH(OCH_3)_3$ the ratio

of the stereoisomeric alcohols formed depends on the concentration of the reagent:

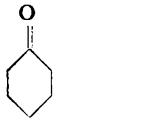
0.01 mole — 28 % — 72 %
0.50 mole — 63 % — 37 %

The data obtained in recent years point to the necessity of a more careful treatment of the results of reactions even with such a reagent as sodium borohydride. It appears that reactions involving this reagent may alter the steric configuration of centres adjacent to the carbonyl group being reduced (79):

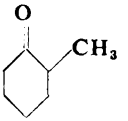



A reagent of high stereoselectivity is lithium *tris-sec*-butylborohydride, $LiBH(C_4H_9\text{-}sec)_3$. Under the action of this reagent 2-methylcyclohexanone gives *cis*-2-methylcyclohexanol which is 99 per cent stereochemically pure; the reduction of 2-methylcyclopentanone has been found to give the same result (80).

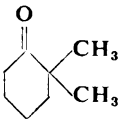
The reduction of a large group of ketones of the cyclohexane series with lithium borohydride has also been studied (81) and the following relative rates of reduction have been obtained (enclosed in parenthesis are the ratios of the *cis-trans* isomers formed):



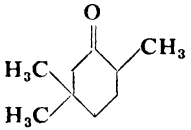

100



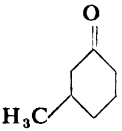

18 (40/60)



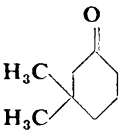

4.4



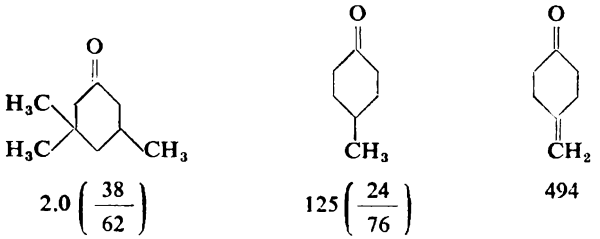

0.30 (71/29)




76 (77/23)

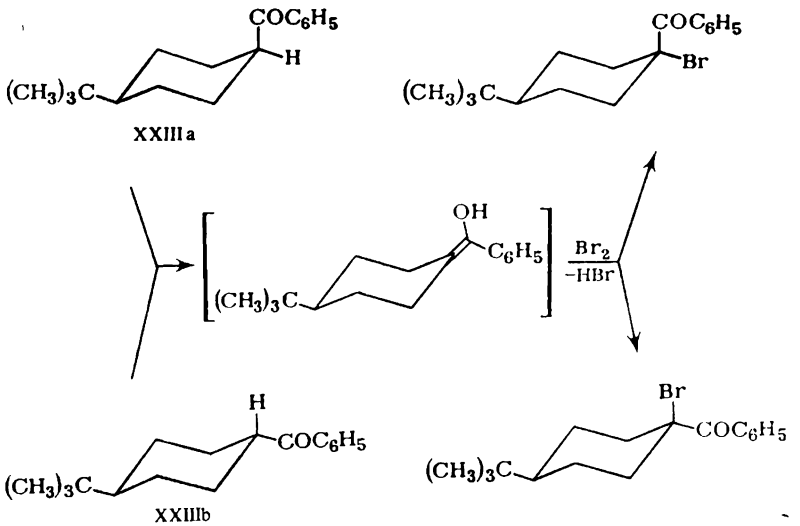



2.3




The results obtained show that sterically hindered ketones are reduced at a lower rate—the substituents in positions 2 and 3 with respect to the carbonyl group slow down the reaction but the ratio of the *cis-trans* products has been clearly shown to be determined not only by steric hindrance.

Ketones XXIIIa and XXIIIb which have a benzoyl group in the axial and equatorial positions, respectively, on bromination with a solution of bromine in carbon tetrachloride give a mixture of axial and equatorial bromoketones in the ratio of 1 : 1 (82). This is evidence that the bromination occurs via the same intermediate enol:

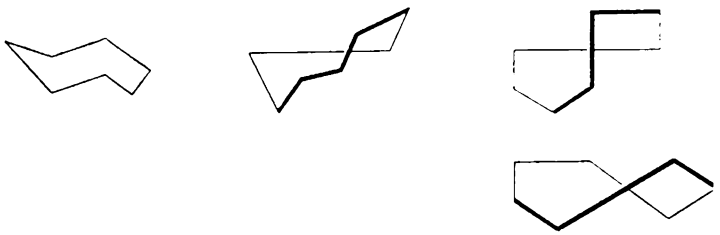



But if the reagent contains about 1 per cent of alcohol, the bromination of XXIIIa yields the same result, while the bromination of XXIIIb gives

80 per cent of equatorial bromoketone. The mechanism of bromination of compound XXIIIb is thought to be changed in the presence of alcohol.

## 5.5. CYCLOHEPTANE AND ITS DERIVATIVES

Compounds with a seven-membered ring have been studied to a much lesser extent than those with a six-membered ring. The chair conformation is considered to be the most stable conformation for cycloheptane. According to more recent data, one should better speak of the twist-chair or twist-boat conformation, both of which are in a state of pseudorotation (just like the cyclopentane ring):

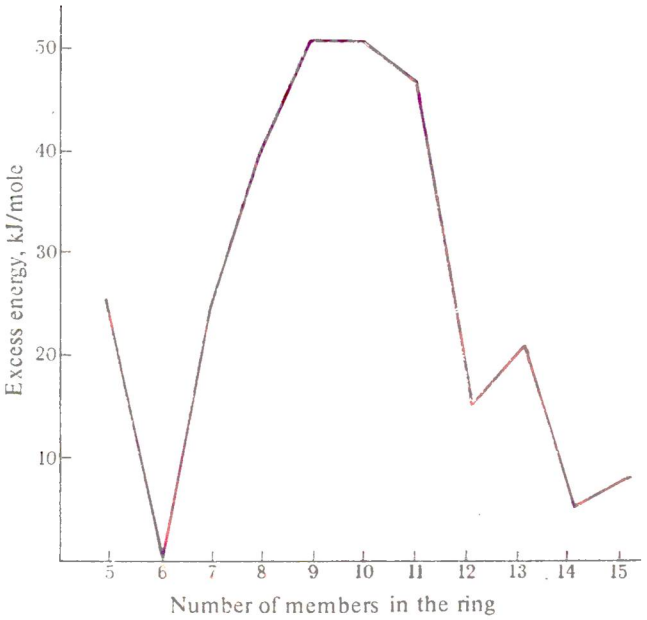


The barrier separating the chair and boat forms is much lower in cycloheptane than in cyclohexane (36 and 53 kJ/mole, respectively). The two forms of cycloheptane (not one form, as in the case of cyclohexane) are conformationally flexible. As a result, the energy difference between the *cis*- and *trans*- isomeric disubstituted cycloheptanes is smaller than that between the corresponding cyclohexane derivatives. Cycloheptane derivatives with two different substituents may exist in 20 and more conformations, and therefore the study of the conformational equilibrium in such compounds presents quite formidable difficulties (83).

## 5.6. MEDIUM RINGS

Compounds with medium-sized rings (8- to 11-membered) are not simply intermediate between common and large rings. While common and large rings generally differ little in chemical behaviour from their aliphatic counterparts, both saturated and unsaturated, the medium rings have specific features that are characteristic only of them and are not encountered in any other class of organic compounds. Detailed reviews on medium rings are available in the literature (84).

Figure 5.7.



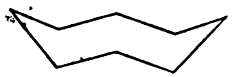

*Excess enthalpy of cyclic compounds (as compared with the infinite polymethylene chain) as a function of the number of carbon atoms in the chain, n.*

Medium rings are characterized by a high energy content (Fig. 5.7). Figure 5.7 clearly shows that 8- to 11-membered cycloalkanes have an increased energy content.

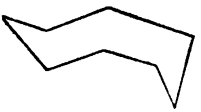
The models demonstrate that medium-sized rings have no angle (Baeyer) strain and are built up of staggered conformations, i.e., they are also free from Pitzer strain. The factor responsible for the increased energy content of such rings is the intramolecular overcrowding, as the result of which the non-bonded atoms are forced to arrange themselves at distances smaller than the sum of their van der Waals radii. This type of strain was called earlier (see page 308) the Prelog strain. The strain per one $CH_2$ group is 5.0 kJ/mole in cyclooctane, 5.9 kJ/mole in cyclononane, 5.0 kJ/mole in cyclodecane, and 4.2 kJ/mole in cycloundecane. In cyclododecane the strain is only 1.3 kJ/mole per $CH_2$ group, which clearly indicates that this ring does not belong to the category of medium-sized rings: it is the first representative of macro (or large)

rings. A rather large body of data have been obtained on the conformations of medium-sized rings.

The most probable conformation for **cyclooctane** was believed at one time to be the extended crown XXIV; more recent works (85) have shown that there exists the boat-chair form XXV in the series of crystalline derivatives of cyclooctane.

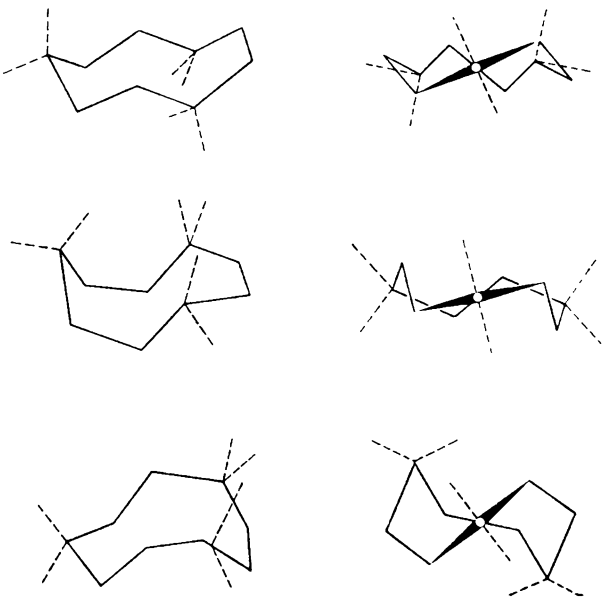


XXIV



XXV

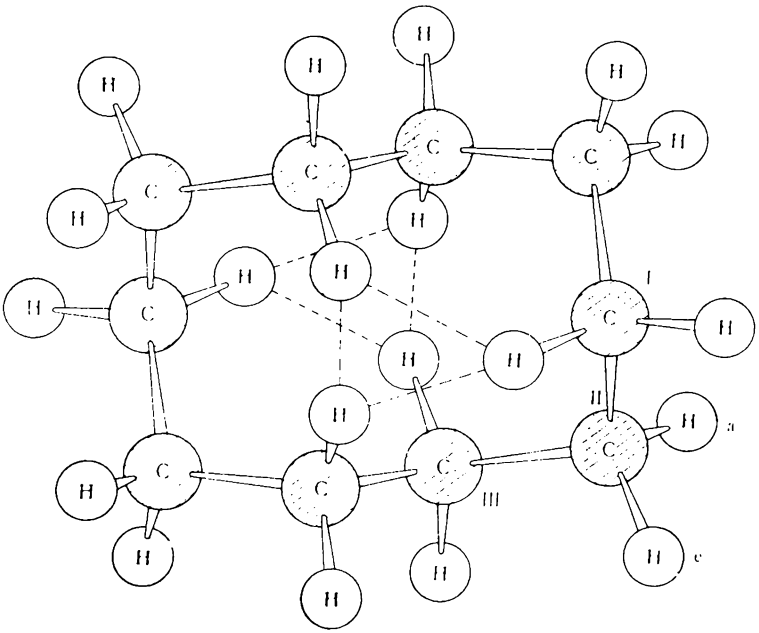
The similar conformations are also believed to exist for cycloheptane, cyclodecane (86). The conformations of cyclononane are combinations of chair and twist-boat forms (87):



We shall now examine, in more detail, the conformational features of **cyclodecane** which is a typical representative of medium rings. In contrast to cyclohexane, all the carbon atoms of which are equivalent, in cyclodecane three different types of carbon atoms may be differentiated (see below). The hydrogen atoms in cyclodecane may occupy six differ-

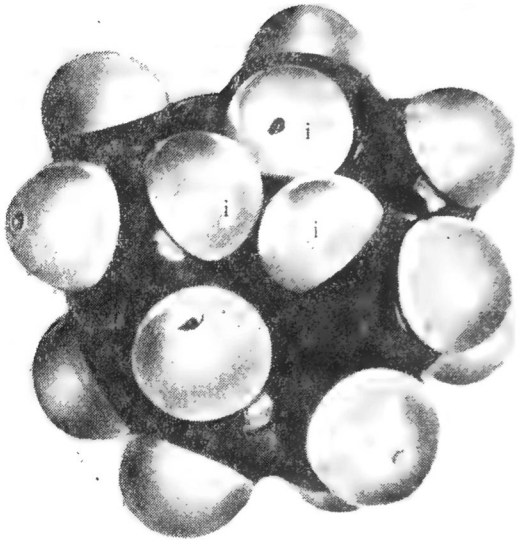
ent positions (instead of two positions, axial and equatorial, in cyclohexane).

One of the important distinctive features of medium-sized rings is the possibility of existence of conformations in which some of the bonds of carbon atoms are directed *into the ring*. Such bonds (and, accordingly, substituents) are termed **intraannular bonds** (or substituents); the bonds (and substituents) arranged outside the ring are called **extraannular** or **peripheral.** Cyclodecane in its most favoured conformation has 6 intraannular and 14 peripheral hydrogen atoms.



From this it follows that the $CH_2$ groups in cyclodecane are stereochemically non-equivalent: among them there are such groups in which both hydrogen atoms are peripheral (type II); there are also such groups in which one hydrogen atom is peripheral and the other is intraannular (types I and III). The last two types differ from each other in that in one case the peripheral hydrogen is equatorial (type I) and in the other, axial (type III). In the space-filling model of cyclodecane are clearly shown the intraannular (designated as *i*) and peripheral hydrogen atoms (see the model on page 360).

Fig. 5.8



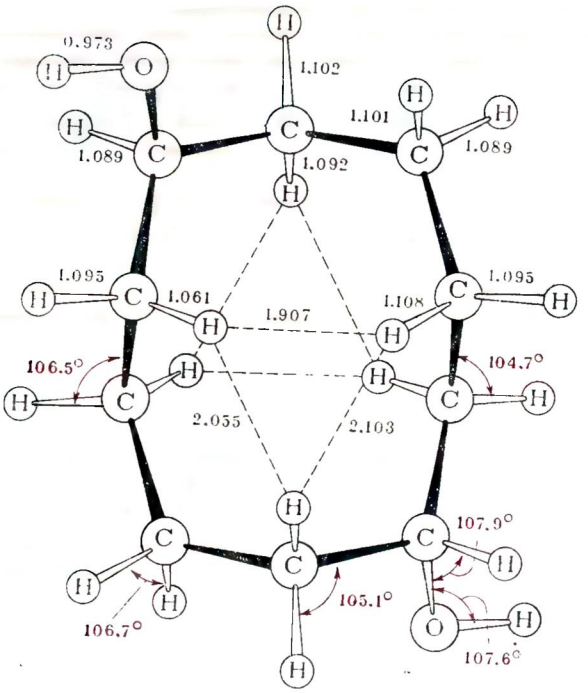

The intraannular hydrogen atoms are arranged in two layers (the upper and the lower) which form two superimposed triangles (on the scheme given on page 359 the hydrogen atoms belonging to the same layer are connected by dashed lines). It is intraannular hydrogen atoms that create intramolecular overcrowding which is responsible for the increased energy of the cyclodecane molecule; this is distinctly seen on the model given in Fig. 5.8 (such hydrogen atoms of the same layer are designated by the letter *i*).

The distances between intraannular hydrogens of the same layer, as determined from the model, are equal to 1.84 Å (the sum of the van der Waals radii being 2.4 Å). The experimental X-ray diffraction determination of these distances in a crystal of *trans*-cyclodecane-1,6-diol gave the values 1.91 and 1.98 Å for the two conformations existing in crystals (Fig. 5.8) (88).

Substituents larger than hydrogen atoms cannot generally occupy intraannular positions. On monosubstitution there are 7 conformers possible — three enantiomeric pairs (substituents in positions II*a*, II*e*, III) and one achiral conformer (the substituent in position I).

For *cis*-1,6-disubstituted derivatives there exists only one pair of enantiomeric conformers; for *trans*-1,6-disubstituted compounds there may exist four achiral conformers: it is believed that two of these confor-

Figure 5.8.




*The structural parameters of trans-cyclodecane-1,6-diol according to X-ray diffraction data (the bond lengths are given in Å).*

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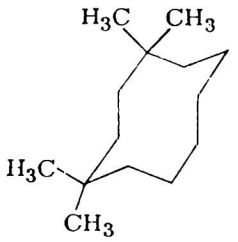
mers give rise to two crystalline forms observed for *trans*-1,6-diaminocyclodecane and for *trans*-cyclodecane-1,6-diol mentioned above. For 1,1,4,4-tetramethylcyclodecane there is only one favoured conformation in which all the $CH_3$ groups are extraannular (89):

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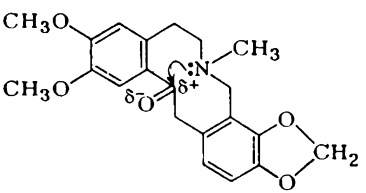
The same conformation, with all the substituents being peripheral, may exist for 1,1,3,3- or 1,1,6,6-tetrasubstituted cyclodecanes. If the substituents are located in the 1,1,2,2- or 1,1,5,5-positions, then one of them should have been intraannular for the usual conformation of the cyclodecane ring. Since this would lead to a considerable increase of the energy of the molecule, the cyclodecane ring adopts a different conformation, which is observed for example, in the case of 1,1,5,5-tetramethylcyclodecanecarboxylic acid (90).

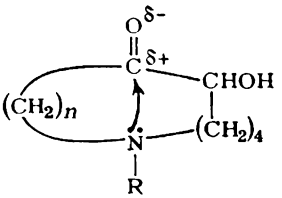
Removal of one of the intraannular hydrogens lowers the internal energy of cyclodecane, especially if this hydrogen belonged to an atom of type III. Therefore, trigonal carbon atoms (the carbonyl group, the exocyclic double bond, the carbonium ion) or hetero-atoms (nitrogen, oxygen) occupy a position of type III in a 10-membered ring. This results (91) in a decrease of the distance between two carbon atoms of type III (or, respectively, between the carbon atom and the hetero-atom) which are on opposite sides of the ring (in positions 1 and 5). For cyclodecane itself the corresponding distance is 3.29 Å, for cyclodecanone the $CH_2$—CO distance is 3.04-3.13 Å, and for 1-oxacyclodeca-5-none the O—CO distance is 2.83 Å.

The most interesting distinctive feature of medium-sized rings is the manifestation of **transannular effects** (also known as *transannular interactions* or *proximity effects)* and the occurrence of **transannular reactions.** These effects and reactions do not occur at the carbon chain and do not involve the neighbouring atoms; they take place between atoms on opposite sides of the ring.

Transannular interactions are especially prominent in those compounds in which units of electrophilic and nucleophilic character are opposed in the ring. In this case, there may be observed, as it were, "transannular neutralization", as, for example, in the molecule of the alkaloid cryptopine XXVI which contains a ten-membered ring. Analogous phenomena have been detected in the series of medium-ring azaacyloins XXVII.



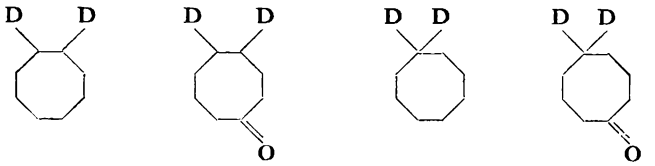

XXVI




XXVII

For optically active compounds of this type, the transannular interaction between nitrogen and the carbonyl group leads, in particular, to the weakening of the Cotton effect (characteristic of the carbonyl group) in the region of 300 nm.

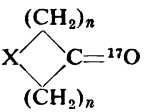
In 1950, Prelog even suggested the idea that the decreased frequency of the vibrations of the CO band in the IR spectrum of cyclooctanone (about 1690 $cm^{-1}$ instead of 1750 $cm^{-1}$) could be explained by the formation of a transannular hydrogen bond to one of the ring hydrogen atoms. To check up this idea, Allinger (92) obtained partially deuterated cyclooctanes and cyclooctanones XXVIII-XXXI:



XXVIII XXIX XXX XXXI

The investigation of the C—D frequencies in the IR spectra of these compounds has shown that they are identical for hydrocarbons (XXVIII and XXX) and ketones (XXIX and XXXI), which is indicative of the absence of an intramolecular hydrogen bond suggested by Prelog and makes more probable the explanation that takes into account the increase of the $O{=}C\langle$ angle in medium-sized rings as compared with the ordinary angle for the carbonyl group in the aliphatic chain.

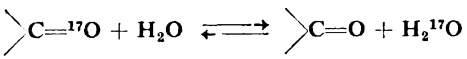
The transannular interaction in 8- and 9-membered ring compounds of the type XXXII has been detected by a change in the chemical shift of $^{17}O$ in the carbonyl group $^{17}O{=}C$ if the ring contains, in addition, an oxygen atom or the group $NC_2H_5$ (93).



XXXII

X = O or $NC_2H_5$

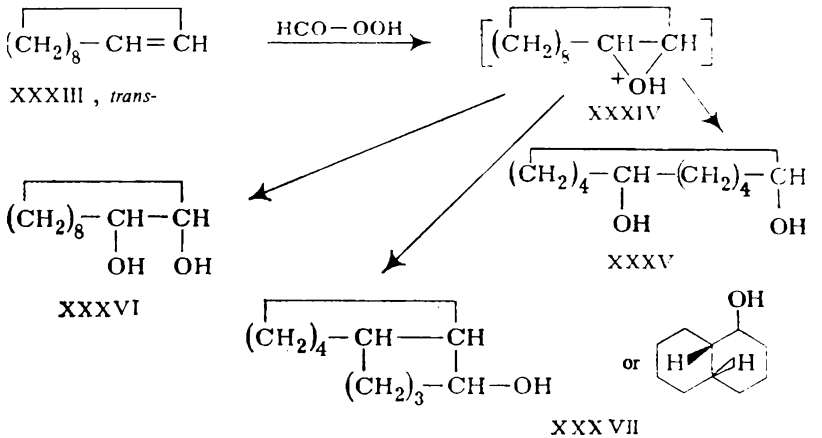
It has also been found that the reactivity of this type of carbonyl group in the hydration reaction decreases (which has also been detected with the aid of $^{17}O$)



The rate of this reaction decreases in going from six- to ten-membered ring compounds; the presence of a hetero-atom X in a six-membered

ring (XXXII, $n = 2$) has *no* effect on the rate of the reaction (there is no transannular interaction in the six-membered ring). But in 8- to 10-membered rings the presence of a hetero-atom sharply lowers the reaction rate, as a result of a transannular interaction.

An example of a specific *transannular reaction* is the oxidation of *trans*-cyclodecene XXXIII with performic acid, which was studied by Prelog in 1952. In this reaction, along with the normal product, cyclodecane-1,2-diol (XXXVI), there are formed a number of other compounds, the most remarkable of which is cyclodecane-1,6-diol (XXXV) and *trans*-1-decalol (XXXVII):

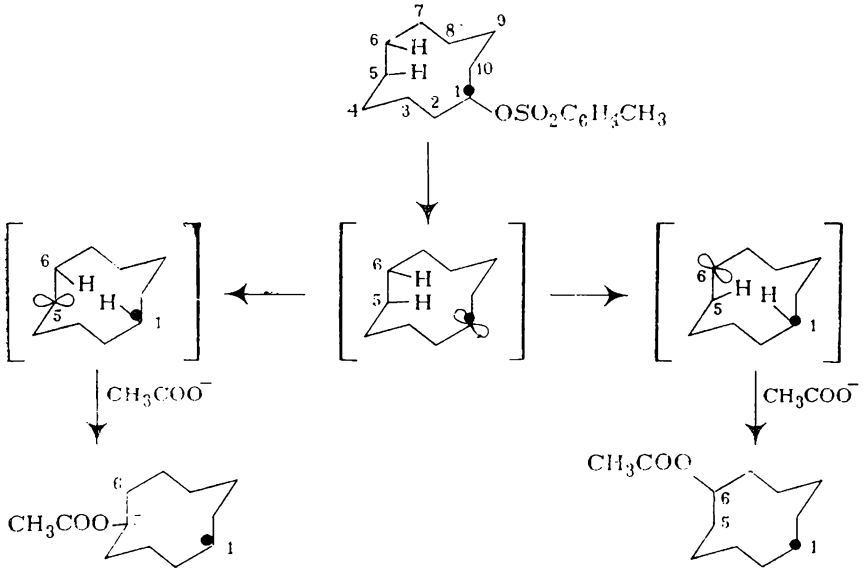



The reaction is believed to proceed via the intermediate cyclic non-classical cation XXXIV which either pulls a hydrogen atom with two electrons from position 6 (to the carbonium ion formed at this site there then adds the hydroxyl anion) or is stabilized due to the formation of a bond between C-1 and C-6 with elimination of $H^+$ and formation of the bicyclic product XXXVII.

The cause of the formation of transannular reaction products can be understood if one recalls the above-considered specific features of the spatial structure of cyclodecane and the transiently formed cyclodecyl cation: in the latter, the positive charge of the carbonium-ion centre is next to intraannular hydrogens that participate in the hydride shift.

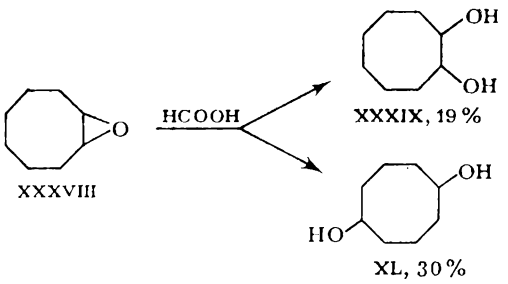
The study of the acetolysis of cyclodecyl tosylate with the aid of labelled carbon has shown that this process too is accompanied by the hydride shifts of intraannular hydrogens from positions 5 and 6 since the entering acetoxy group does not occupy the place of its predecessor, the tosyloxy

group (the labelled carbon is indicated by a red circle on the scheme shown below):




The hydride shift just from positions 5 and 6 (relative to an atom of type III, where the carbonium-ion centre is located) can easily be understood on the basis of the geometry of cyclodecane considered.

Transannular reactions in the cyclooctane series have also been described; for example,




From cyclooctene oxide **XXXVIII**, under the action of formic acid, along with the normal reaction product, 1,2-glycol XXXIX, there is formed 1,5-glycol XL as the result of a transannular reaction. This is a

consequence of a hydride shift similar to that considered for cyclodecane.

The transannular reactions in medium-sized rings have been investigated by many other authors.

A characteristic feature of transannular interactions and reactions is their stereospecificity. This means that if the starting material is a certain spatial stereoisomer, the product of transannular reactions will also be, as a rule, a certain stereoisomer and not a mixture of isomers. This is not surprising since the occurrence of transannular reactions, as we have already seen, is closely associated with the spatial form of the ring.

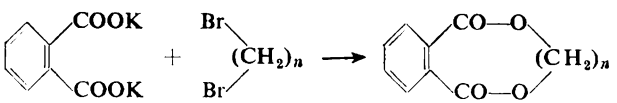
Transannular interactions are the most pronounced in medium-sized rings, but certain manifestations of such interactions may be encountered in other compounds as well. Thus, the signs of a transannular interaction of hydroxyl groups were detected in the analysis of the IR spectra of the cycloheptane-1,4-diol series (94). It is believed (95) that in cyclohexane too there takes place a transannular interaction between the substituents in positions 1 and 4. Some authors believe that a transannular migration of hydrogen may also take place in six-membered rings (96). The homoconjugation effect considered in Chapter 4 (see page 294) is also an interaction across the ring.

## 5.7. LARGE RINGS

Alicyclic compounds with the number of members in the ring exceeding 12 are highly flexible. No *cis-trans* isomers can exist here because of the nearly free rotation about C—C bonds; it is also difficult to freeze definite conformations. It is assumed that large rings exist predominantly in the form of extended rectangles composed of zig-zag conformations. The square form is less favourable because no intramolecular close packing is possible in it.

From the IR spectral data on the cyclic compounds $C_{14}H_{28}$ and $C_{16}H_{32}$ there have been deduced conformations which simulate the arrangement of the carbon atoms in small piece of the diamond crystal lattice (97). The conformations of macrocyclic diketones have also been studied (98).

The stereochemical factors play an important part in reactions leading to the formation of large rings. The approach of the two ends of a long aliphatic chain is improbable and this circumstance makes it difficult to synthesize large rings. It has been found that if the ring-forming fragments are suitably oriented, the closure of a large ring is facilitated (99), as, for example, in syntheses proceeding by the following scheme:



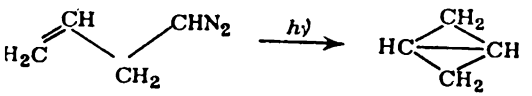

$n = 6$ to 14

## 5.8. CONDENSED-RING SYSTEMS (FUSED-RING COMPOUNDS)

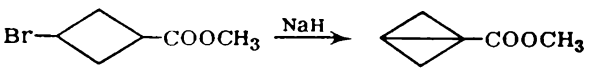
### 5.8.1. SYSTEMS CONSISTING OF SMALL RINGS

It has long been firmly believed that it is pointless to attempt to prepare condensed-ring systems composed of small rings since such structures must be highly strained. In the sixties, however, such attempts proved successful and an entirely new field was unexpectedly offered to the chemist (for a review, see ref. 100).

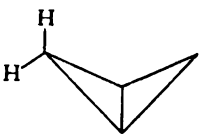
Even such a strained structure as bicyclobutane proved to be capable of existence. It was prepared photochemically from 3-diazobutene:



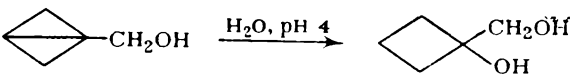
Another route for building up the bicyclobutane ring is also possible:



Other compounds of the bicyclobutane series have also been obtained. Their geometric form is represented as follows:



Just as in the case of cyclopropane, here too the structure is built up by means of banana bonds. The hydrogens of $CH_2$ groups are classed into two types, resembling the *exo*- and *endo*-positions in derivatives of bicyclo[2.2.1]heptane. The central bond is chemically extremely active, which may be illustrated, for example, by the following reactions:



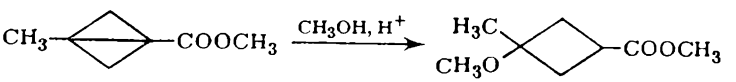
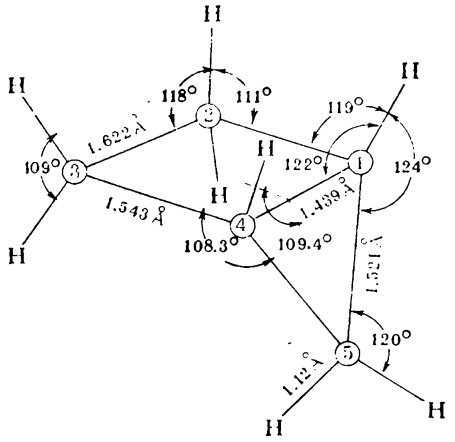


Figure 5.9.




*The structural parameters of bicyclopentane according to X-ray diffraction data.*

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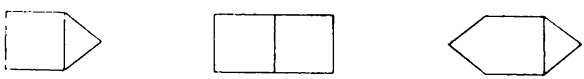
The next homologue must contain a condensed-ring (fused-ring) system made up of one three-membered ring and one four-membered ring. Such a compound is known to exist; this is bicyclopentane. There is no need to detail its name by adding the code numbers (as is done in the Baeyer system) since only one isomer, XLI, can exist. According to the data of electron-diffraction studies (101), bicyclopentane has the geometric parameters given in Fig. 5.9. The entire molecule has the opened-envelope form; the cyclobutane ring is planar, the ring puckering between the planes of the four- and the three-membered rings is about 109.4°. The unusual lengths of some of the bonds attract our attention: the bond between C-2 and C-3 is unusually long and the bridge bond between C-1 and C-4 is the shortest of those observed in saturated compounds.

Further consideration of similar condensed-ring bicyclic systems leads us to a bicyclic compound consisting of two four-membered rings, bicyclo[2.2.0]hexane XLII (103). The numbers that indicate the detailed structure are necessary here because there is one more isomer, bicyclo-[3.1.0]hexane XLIII (104).



XLI XLII XLIII

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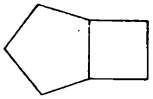
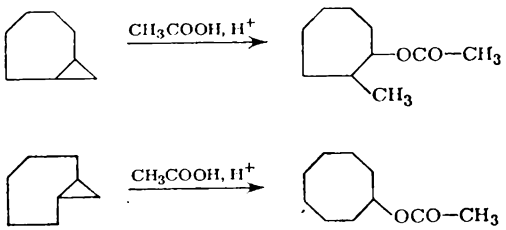


XLIV

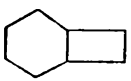
XLV

The next homologues, isomeric bicycloheptanes, have also been studied: bicyclo[3.2.0]heptane XLIV (105) and bicyclo[4.1.0]heptane XLV (106).

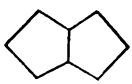
A characteristic stereochemical feature of the fused-ring bicyclic systems under consideration is that the rings are joined together only by the *cis*-junction. Starting from bicyclooctanes, the *trans*-junction of rings becomes possible. Thus, bicyclo[5.1.0]octane is capable of existing in two stereoisomeric forms. It is interesting that the stereoisomeric forms when subjected to acetolysis give different reaction products: a seven-membered ring is formed from the *cis*-isomer and an eight-membered ring from the *trans*-isomer (107):




Other isomeric bicyclooctanes (162) are bicyclo[4.2.0]octane XLVI and bicyclo[3.3.0]octane XLVII; the latter compound is known under the trivial name pentalane.



XLVI



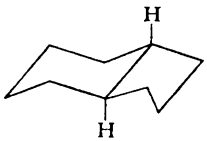
XLVII

There exist two stereoisomers of XLVII, of which the *trans*-isomer is the less stable; the enthalpy of its formation is 25 kJ/mole greater than that for the *cis*-isomer.

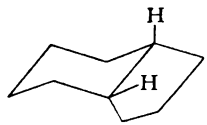
The general specific feature of all condensed-ring structures built up of small rings is their high strain. The strain energy in bicyclobutane is 270 kJ/mole; in bicyclopentane it is 230 kJ/mole. It is reported that in the USA, structures of this type have attracted the attention of jet-fuel specialists because of their great energy content.

5.8.2. HYDRINDANE

The *cis-trans* isomers of bicyclo[4.3.0]nonane, which is known as hydrindane, have been studied rather thoroughly.

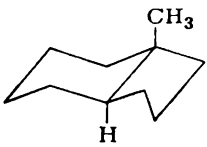



*trans-*

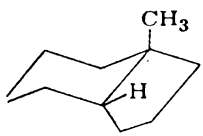



*cis-*

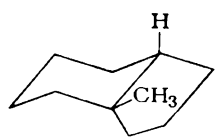
The fusion of rings in the *trans*-isomers is realized by means of two equatorial bonds; the junction in *cis*-hydrindane is equatorial-axial. The difference in formation enthalpy is about 5 kJ/mole in favour of the *trans*-isomer (in the gaseous phase). The small energy difference existing between the *cis*- and *trans*-isomeric hydrindanes can be further reduced or even changed in favour of the *cis*-isomer by addition of substituents. Thus, according to calculations (108), the energy of stereoisomeric 8-methylhydrindanes decreases in the following sequence:




*trans-*




*cis-* (steroid form)



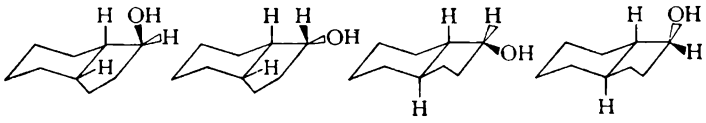

*cis-* (non-steroid form)

The *cis*-isomer exists in two stereoisomeric modifications: the methyl group is axial in the "steroid form" and equatorial in the "non-steroid form". These terms are used because hydrindane simulates the C and D rings of steroids.

For the ketone 1-hydrindanone the more stable is the *cis*-isomer. Introduction into the ketone molecule of a double bond at position 5 or of a methyl group at position 4 renders the *trans*-isomer more stable.

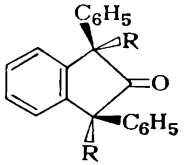
The introduction of a substituent into the hydrindane ring at any position, except for the junction atoms, increases the number of possible spatial isomers up to eight; not only the carbon atom at which the substitution has taken place but also the junction atoms of a bicyclic compound become asymmetric. The 8 stereoisomers obtained give rise to

4 racemates. Stereoisomerism of this kind has been thoroughly studied by Hückel (109) on 1-hydrindanols:

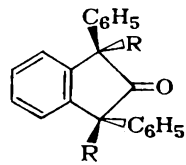


| | | | | |
|---|---|---|---|---|
| M.p. ..... | 18°C | 44°C | 52°C | (liquid, b.p. 115°C) |
| M.p. of 3,5 dinitrobenzoates | 91°C | 125°C | 137.5°C | 101-102°C |
| M.p. of tosylates..... | 42.2°C | 64°C | 47°C | 23-25°C |

The aromatization of the six-membered ring of hydrindane gives **indane,** the stereoisomerism of which can be caused only by substituents in the five-membered ring. Thus, 1,3-diphenyl-2-indanones (XLVIII, R = H, $CH_3$) exist in *cis-trans*-isomeric forms (110):

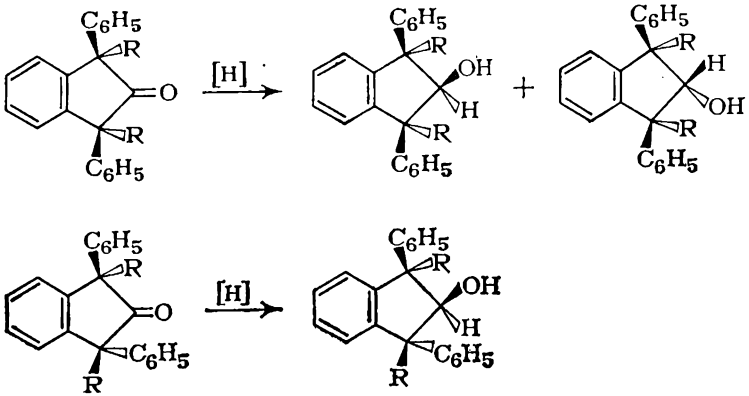


XLVIII a



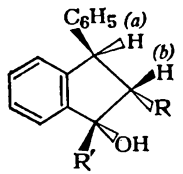
XLVIII b

The *cis*-isomer XLVIIIa is a *meso*-form and the *trans*-isomer XLVIIIb is a racemate which can be resolved into optical antipodes; this difference can be used for configuration determination. Another difference between these *cis-trans* isomers is that the *cis*-form XLVIIIa on reduction gives two diastereomeric alcohols, whereas the *trans*-form XLVIIIb gives only one:

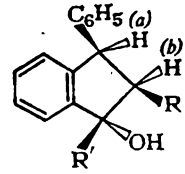


The reduction products differ in PMR spectra: in the alcohols obtained from the *cis*-form, the substituents (say, with R = $CH_3$) are equivalent and give one signal ($\delta_{CH_3}$ = 1.75 ppm). The substituents in the reduction product of the *trans*-form are diastereotopic and therefore give two signals ($\delta_{CH_3}$ = 1.73 and 1.22 ppm).

Substituted indanols with the hydroxyl group in position 1 have also been investigated (111). The *cis-trans*-isomeric compounds have different conformations which can be distinctly differentiated by the NMR spectra:




*trans*-, $J_{(a)(b)}$ = 9-11 cps

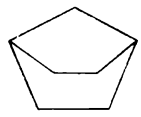



*cis*-, $J_{(a)(b)}$ = 7-7.5 cps

### 5.8.3. NORBORNANE (BICYCLO[2.2.1]HEPTANE)

Bicyclo[2.2.1]heptane is a very important compound since it forms the basis of natural bicyclic terpenes (borneol, camphor, etc.). The trivial name of this compound, **norbornane**, is derived from the name of one of these terpenes; this name is often used instead of the systematic name.

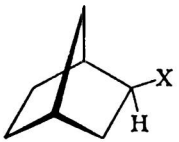
The skeleton of norbornane is built up of the cyclohexane ring in the boat form, to the "raised" atoms of which is connected a bridge consisting in this case of one carbon atom:



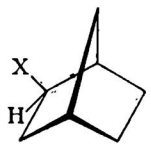
or in a different projection

The bridge can be closed only when the bond angles are slightly distorted. Besides, the pairs of carbon atoms at the bottom of the boat have the eclipsed conformation, which also makes a certain contribution to the development of strain in the norbornane structure.

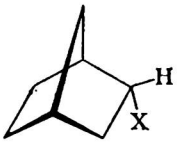
Unsubstituted bicyclo[2.2.1]heptane is symmetric, but as soon as a substituent appears in any of the $CH_2$ groups (except for the bridging group) the system loses the elements of symmetry, just as is the case with hydrindane:



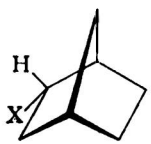

XLIXa




XLIXb




XLIXc

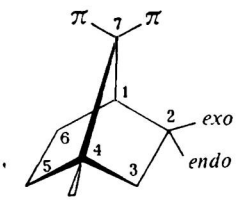



XLIXd

Not only the atom to which the substituent is attached is asymmetric but both bridgehead atoms are also asymmetric. The number of stereoisomers, however, is not 8 ($2^3$) but only 4 because the configuration of both bridging atoms can be changed only *simultaneously* because of the rigidness of the system. This may give rise only to the following combinations (the configuration of the individual asymmetric centres is designated by the *R,S*-system, assuming that X is a substituent with an atomic number greater than that of carbon):

| Formula | Configuration of bridgehead atoms C-1 | C-4 | Configuration of the substituted atom C-2 |
|---|---|---|---|
| XLIXa | S- | S- | S- |
| XLIXb | S- | S- | R- |
| XLIXc | R- | R- | R- |
| XLIXd | R- | R- | S- |

The valences (the valence bonds of carbon atoms) that do not participate in the formation of a ring are classified into *four* types according to their orientation relative to the ring. In accordance with this, in monosubstituted bicyclo[2.2.1]heptanes the substituent may occupy four different positions:

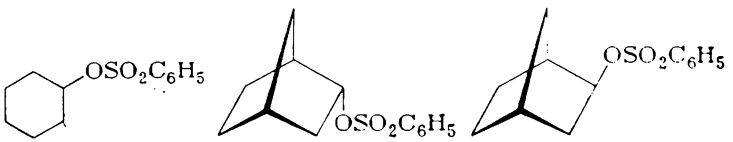



Bridgehead position

At atoms C-1 and C-4 there is only one bond left, which does not participate in the formation of the ring. The substituents that are in these positions are usually said to stand at the bridging atoms or at the bridgehead. The atoms 2, 3, 5 and 6 each have two exocyclic valencies which sharply differ by their spatial orientation; they are termed the *exo*- and *endo*-positions. The former resembles the equatorial and the latter, the axial positions in cyclohexane. The *endo-exo* forms of substituted bicyclo[2.2.1]heptane are actually existing stable spatial isomers. This distinguishes them from the *a*- and *e*-forms of monosubstituted cyclohexanes, in which there is only a conformational difference, i.e., the two forms are rapidly interconverting and are at equilibrium. The exocyclic valencies of the bridging carbon atom differ in spatial orientation from all the others. The groups that are situated at atom C-7 are sometimes called π-substituents.

The rigidity of the norbornane skeleton provides the locking of substituents introduced in a strictly definite position. In this connection, compounds having the skeleton of bicyclo[2.2.1]heptane are preferred as models for investigating the stereochemistry and mechanisms of reactions.

Isomeric compounds in which the substituents are either in the *endo*- or *exo*-position and also at the bridgehead differ significantly in reactivity. This may be illustrated by a comparison of the rates of hydrolysis of esters:

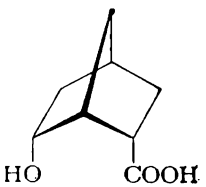



L 1.0 LI 1.4 LII $3.5 \times 10^5$

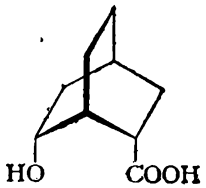
The rate of saponification of the ester of isoborneol, LII, exceeds by 250,000 times (!) the rate of saponification of the corresponding ester of borneol, LI. It is important to note that here we are dealing with an enormous *increase* of the rate of hydrolysis of esters of cyclic alcohols, and the reference unit is the rate of hydrolysis of cyclohexanol derivatives. The phenomenon of accelerations under the influence of neighbouring groups is termed **synartetic** (or **anchimeric**) **acceleration.** The rates of racemization and exchange of oxygen in acid medium also differ for isoborneol and borneol by $2.3 \times 10^5$ times (112).

Interesting observations have been made for compounds of the norbornane and bicyclo[2.2.2]octane series: the reaction rates are strong-

ly dependent on slight changes in the spatial orientation of substituents (113). The related hydroxy acids LIII and LIV were compared.




LIII

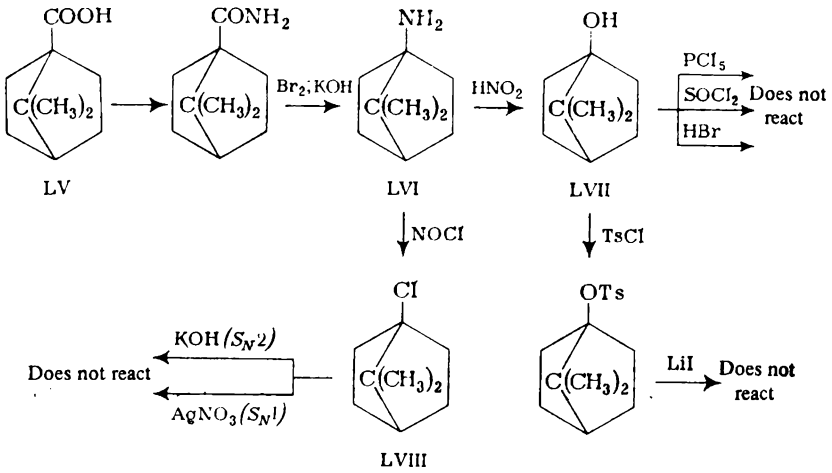



LIV

The norbornane derivative LIII undergoes lactonization 1000 times faster than a derivative of bicyclo[2.2.2]octane, LIV, though the distance between the functional groups in both compounds is practically the same. At the same time, the rates of hydrolysis of both lactones differ little; their IR spectra are also closely related.

Of great interest are the nucleophilic substitution reactions at the bridging atom of bicycloheptane systems. Theoretically it may be expected that the rigidity of the skeleton must hinder Walden inversion and, hence, prevent the occurrence of $S_N2$ reactions. But for $S_N1$ reactions too the conditions are unfavourable since the skeleton rigidity prevents the formation of a planar carbonium ion.

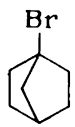
An experimental testing of the validity of theoretical inferences as to the inertness of substituents at the bridgehead towards nucleophilic substitution reactions was undertaken by Bartlett in the thirties. Using 1-carboxyapocamphane LV as the starting compound, he carried out the following conversions:



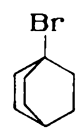
Having prepared 1-apocamphylamine (LVI) by the Hofmann reaction, Bartlett converted it, by the action of nitrous acid, into the alcohol LVII and then into the chloride LVIII by the action of nitrosyl chloride. Compound LVIII was found to be inert both in $S_N1$ reactions (boiling with an alcoholic solution of silver nitrate for 48 hours failed to lead to the replacement of the halogen atom by the nitro group) and in $S_N2$-type reactions (the attempt to carry out a saponification reaction by boiling it for 24 hours with 30-percent solution of KOH gave a negative result). The alcohol LVII was also found to be incapable of entering into $S_N2$-type reactions; its tosylate failed to react with lithium iodide.

The interaction of apocamphylamine LVI with nitrous acid and nitrosyl chloride, which resulted in the formation of alcohol LVII and chloride LVIII, respectively, probably proceeds by the so-called $S_Ni$-type mechanism—a nucleophilic substitution with retention of configuration without the participation of the neighbouring group.

Under more severe conditions there can probably be effected $S_N1$ reactions at the bridgehead. For instance, 1-bromobicycloheptane LIX when heated at 150°C with an aqueous solution of $AgNO_3$ for two days is converted into the corresponding alcohol. More facile is the analogous conversion of 1-bromobicyclooctane LX, which requires only 4-hour boiling.




LIX

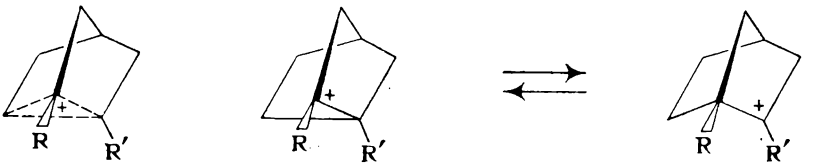



LX

Evidently, in these reactions there is formed a "nearly planar" carbonium ion. The greater ease with which the reactions of compound LX proceed is accounted for by the greater flexibility of the bicyclooctane system. The reactions at the bridgehead atom of bridged systems have been thoroughly studied by Applequist and Roberts (114).

It is well known that one of the most remarkable features of compounds having the bicycloheptane skeleton is their ability to undergo carbon-skeleton rearrangements. These and other reactions are highly stereospecific even when the transition states are symmetrical structures. In this connection, the reactions of norbornane compounds are said to display the so-called "memory effect" (see ref. 115). Many of the specific features of the reactions of norbornane compounds have been explained by the participation of "non-classical ions"—carbonium ions (carbocations) in which the charge is distributed over several ring carbon atoms. This conception, however, was later critisized. In 1972

there was published a work (116), the author of which claimed to have obtained, by means of NMR spectra, an irrefutable physical proof that not the "non-classical ions" LXIa but the isomeric cations LXIb and LXIc, which are at equilibrium, participate in these reactions.

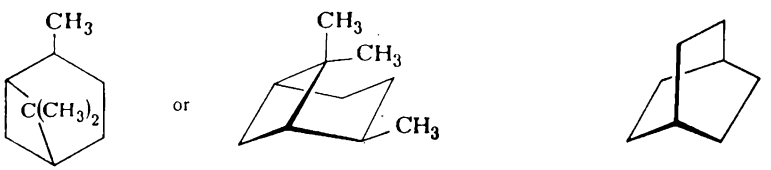



LXIa LXIb LXIc

Compounds having the skeleton of bicyclo[2.2.1]heptane occur in nature in optically active forms: such are borneol and camphor in the first place. Owing to the ready availability of these optically active compounds they are important starting materials for the preparation of asymmetric reagents (see Chapter 2, page 97). The optical activity of compounds of this type has been and is extensively studied.

### 5.8.4. OTHER BRIDGED-RING STRUCTURES

The cyclic system of bicyclo[3.1.1]heptane forms the basis of the pinane ring LXII found in terpene compounds:



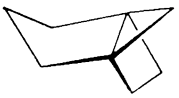

LXII LXIII

We shall not discuss this structure in detail; instead, the reader is referred to works devoted to the study of the conformations and configurations of pinane derivatives by means of present-day methods (117).

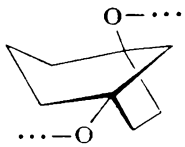
The specific features of the symmetry of bicyclo[2.2.2]octane LXIII are such that the difference between the *exo*- and *endo*-positions disappears and there are left only two possibilities for the isomerism of mono-

substituted derivatives to be displayed: with a substituent at the bridging atom or in any other position.

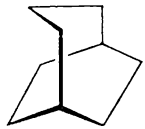
**Propellane** (the trivial name of tricyclo[3.2.1.$0^{1,5}$]octane LXIV) may be regarded as a structure built up of three-, four- and five-membered rings. The highly strained state of this structure manifests itself, for example, in that under the action of oxygen there takes place a reaction with the formation of a polymeric peroxide LXV.



LXIV




LXV

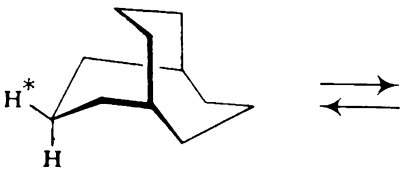


LXVI

The next homologue, bicyclo[3.2.2]nonane LXVI, can be built free of angle strain. Information on the derivatives of this cyclic system is available in the literature (118).

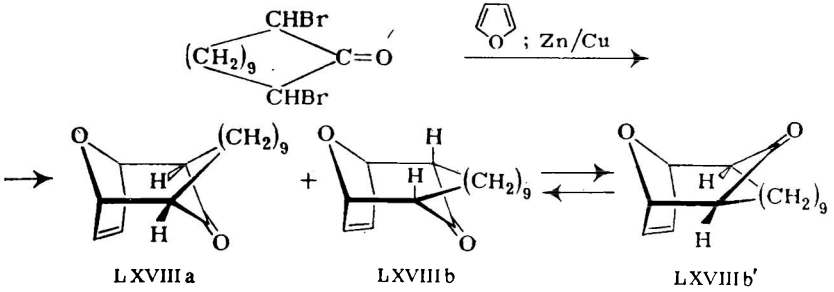
Bicyclo[3.3.3]undecane (the trivial name is **manxane**) LXVII is composed of 8-membered rings which display considerable conformational mobility. A study of this ring by means of NMR spectroscopy has shown that all the hydrogen atoms of its $CH_2$ groups are equivalent. Incidentally, with the fixed conformation of the ring the presence of two types of hydrogen atoms, resembling the *exo*- and *endo*-hydrogen atoms of norbornane, should be expected. This led to the conclusion that manxane exists in two readily interconvertible conformations (119). The barrier between them (at —60°C) is about 40 kJ/mole.

LXVII




The complex bridged-ring structure LXVIII has attracted the attention of investigators (120) because the existence of two conformers,

LXVIIIb and LXVIIIb′, has been detected in one of the isomers, LXVIIIb, by means of PMR spectroscopy.




LXVIIIa LXVIIIb LXVIIIb′

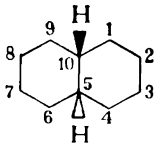
In the isomer LXVIIIa, the six-membered oxygen-containing ring has the chair form, and instead of the 1,3-axial hydrogens, the nonamethylene bridge is attached to this chair form. This structure is a stable isomer isolable as an individual compound. The other isomer, LXVIIIb, as indicated by PMR data, consists of two conformers in equilibrium with each other. One of them, LXVIIIb, has the pyran ring also in the chair form, but the nonamethylene bridge is attached equatorially; the other conformer, LXVIIIb′, has the pyran ring in the boat form. The equilibrium between these conformers may be shifted to either side, depending on the nature of the solvent.

### 5.8.5. DECALIN

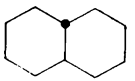
Extensive studies have been devoted to the stereochemistry of bicyclo-[4.4.0]decane which is widely known by the name **decalin.** This compound exists as two stereoisomers: *cis*- and *trans*-decalins. The existence of two stereoisomeric decalins required by the non-planar structure of the cyclohexane rings was predicted by Mohr. Shortly after this, Hückel (121) obtained both stereoisomers; they are characterized by the following constants:

| | *cis*-Decalin | *trans*-Decalin |
|---|---|---|
| Boiling point, °C | 193 (at 743 mm Hg) | 184.5 (at 747 mm Hg) |
| $d_4^{20}$ | 0.895 | 0.870 |
| $n_D^{20}$ | 1.4811 | 1.4697 |
| Heat of combustion, kJ/mole | 6285 | 6271 |

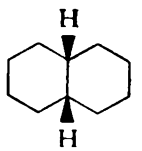
*cis*- and *trans*-Decalins are spatial isomers existing in the form of stable individual compounds with a rigid, fixed conformation. They are usually represented in a conventional planar form (the hydrogen situated above the ring plane is marked with a dot):



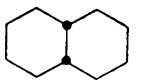

or



*trans*-

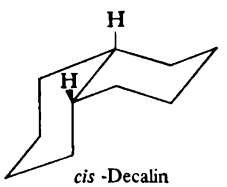



or

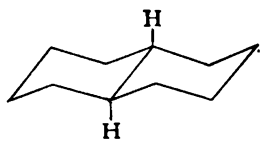


*cis*-

According to the original hypothesis put forward by Mohr, it was assumed that one of the decalins was composed of cyclohexane rings in the chair conformation, the other having the boat conformation. Later, however, it was proved that the two isomers are built up of rings in the chair form (122):




*cis* -Decalin
(*a,e*-ring junction)

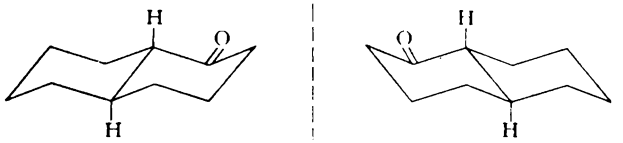



*trans*-Decalin
(*e,e*-ring junction)

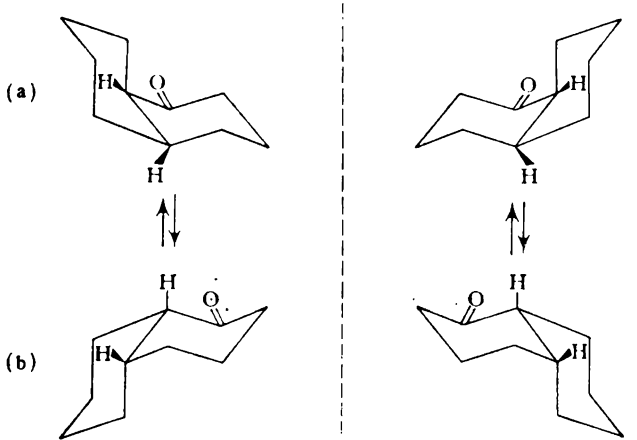
The heats of combustion given above show that *trans*-decalin is thermodynamically more stable. As evidenced by new data, the difference in enthalpy is 11.4 kJ/mole in favour of *trans*-decalin. When a methyl group is introduced into the angular position (5-methyldecalin), two skew interactions are added in the *trans*-form and only one, in the *cis*-form. This lowers the enthalpy difference down to 3.6 kJ/mole (also in favour of the *trans*-isomer). According to experimental data, at 250°C the equilibrium mixture contains 41 per cent of *trans*-5-methyldecalin and 59 per cent of the *cis*-isomer (123).

Introduction of a substituent at any of the non-common atoms makes not only this atom but also both common atoms asymmetric. Thus, a monosubstituted decalin with the substituent situated at a non-common carbon atom may have 8 stereoisomers which are optically active (cf. hydrindanes).

Introduction into one of the rings of any other "label", which does not render the atom asymmetric, nevertheless creates the asymmetry of the common atoms. As an example, let us consider 1-decalones, for which the existence of stereoisomeric forms can be predicted.

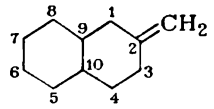


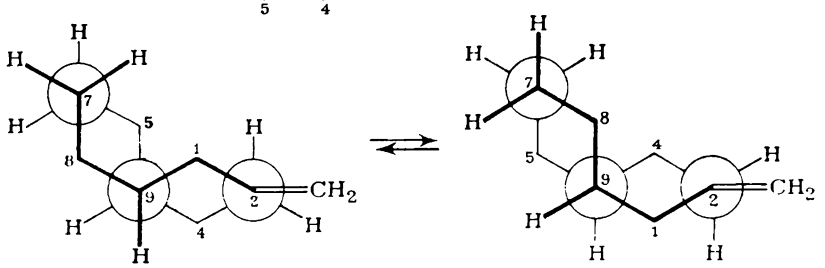
Pair of optical antipodes
of *trans*-1-decalone (*e,e*-ring junction)




Pair of optical antipodes
of *cis*-1-decalone (*a,e*-ring junction)

In contrast to the rigid *trans*-form, the *cis*-form of 1-decalone possesses some conformational mobility: each of the antipodes can exist in two conformations. The difference between these conformations may be formulated thus: in one case (conformation a) the carbonyl group is next to the axially oriented angular hydrogen atom, and in the other (conformation b) it is next to the equatorially oriented hydrogen atom. Such conformers have been established for 2-methylidenedecalin by means of NMR spectroscopy (124):




The energy parameters of this conversion, which is effected by way of rotation about the central $C_9$—$C_{10}$ bond are as follows: the inversion barrier expressed in terms of free energy, enthalpy, and entropy, are, respectively, equal to: $\Delta G^{\neq}$ 52.8 kJ/mole; $\Delta H^{\neq}$ 47 kJ/mole; $\Delta S^{\neq}$ —6 entropy units.

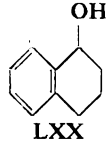
It may be assumed that the energy barrier separating the individual conformers can be increased by introducing appropriate substituents; each of them could then be able to exist as a stable isomer. No such examples are however known at present.

Stereoisomeric 1-decalones and the decalols prepared from them were studied in the thirties in the works of Hückel; certain relationships were established between the various compounds (see the scheme on page 383).

Moreover, *cis*- and *trans*-decalones are capable of interconversion; this refers not only to 1-decalones but to 2-decalones as well. The behaviour of *cis*- and *trans*-2-decalones on heating in the presence of palladium on charcoal shows that an equilibrium sets in between them, in which *trans*-2-decalone predominates (125); it is thermodynamically more stable (the enthalpy difference in the course of *cis-trans* conversion at 498K is $9.2 \pm 2$ kJ/mole). At 200°C the thermodynamically equilibrium mixture consists (to an accuracy of up to $\pm 0.5$ per cent) of 81 per cent of *trans*-2-decalone and $19 \pm 0.5$ per cent of *cis*-2-decalone.

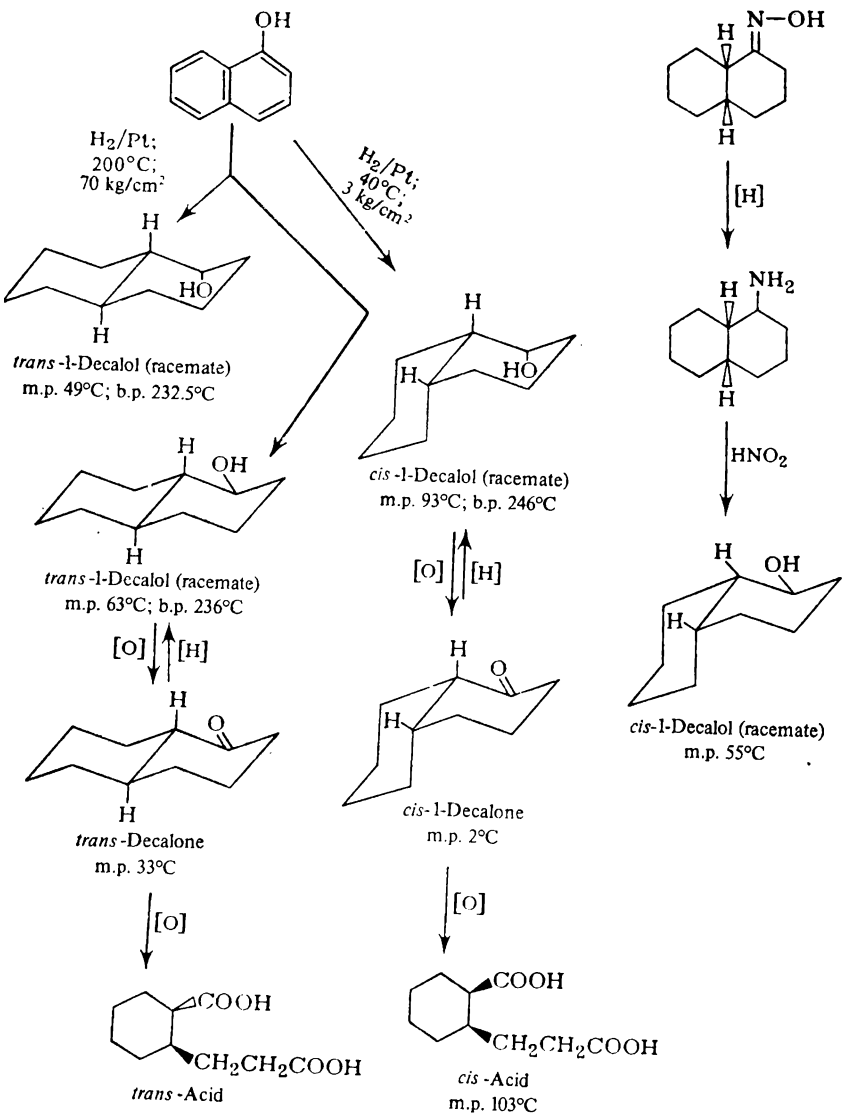
On partial aromatization decalin is converted into **tetralin** (tetrahydronaphthalene) LXIX. In tetralin, no stereoisomerism due to ring-fusion is possible. Stereoisomerism, however, appears in tetralins substituted in the hydrogenated ring. An example is 1-tetralol (LXX). A remarkable feature of this compound is the intramolecular interaction between the hydroxyl group and the aromatic nucleus detected from the IR spectra (191).

LXIX

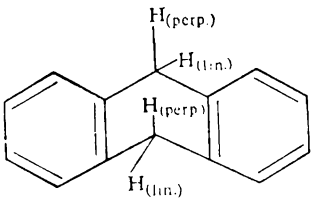



LXX

Tetralins substituted in the alicyclic ring exist in optically active forms, as, for example, 1-tetralol.

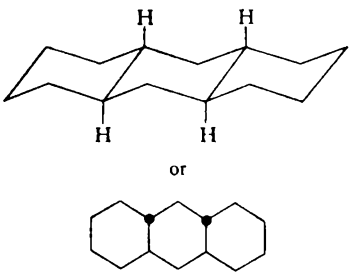


The structure of 9,10-dihydroanthracene is rather specific (127). In this compound, the central (hydrogenated) six-membered ring has the boat form. The angle between the bowsprit and flagpole bonds of the boat (150°) is strongly different from the tetrahedral angle. The valencies of the central carbon atoms, which do not participate in the formation of the ring, have different orientations: linear and perpendicular. The boat form is capable of facile conversion, in the course of which the perpendicular substituent becomes linear and vice versa.

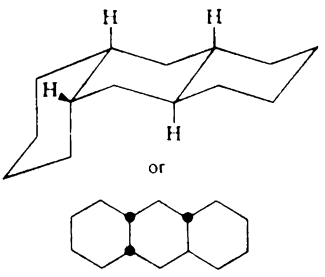



Sterically less hindered is the perpendicular substituent, for which reason the monosubstituted compounds exist in the perpendicular conformation and 9,10-disubstituted *cis*-isomers are more stable than the *trans*-isomers (128).

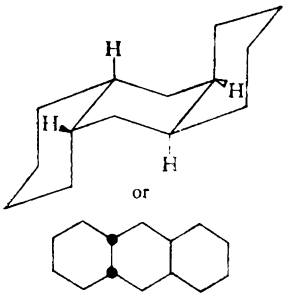
The fully hydrogenated anthracene, **perhydroanthracene,** exists in five stereoisomeric forms due to different ring junctions. They are represented in a planar form below: the dot denotes the hydrogen above the plane of the ring at a ring-fusion atom. The designations *cis*- and *trans*- indicate the ring junction, and the terms *syn*- and *anti*- specify the position of the extreme rings relative to each other:



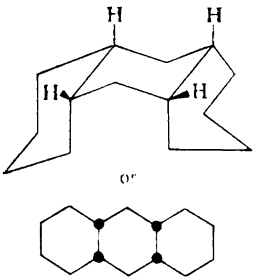

LXXIa, *trans-syn-trans-*



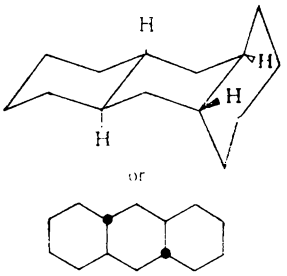

LXXIb, *cis-anti-trans-*




LXXIc, *cis-anti-cis-*




LXXId, *cis-syn-cis-*

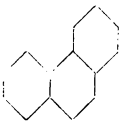



LXXIe, *trans-anti-trans-*

The stability of the stereoisomers decreases from LXXIa to LXXIe. Compounds LXXIb and LXXIe are chiral: apart from the forms given, there also exist their mirror-images—optical antipodes.

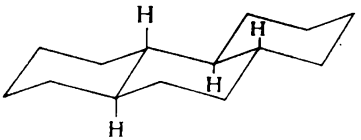
### 5.8.7. PERHYDROPHENANTHRENE

Perhydrophenanthrene LXXII is important as a constituent part of the skeleton of a large class of natural compounds—steroids and related pentacyclic triterpenes (steroids will be discussed in more detail on page 629).

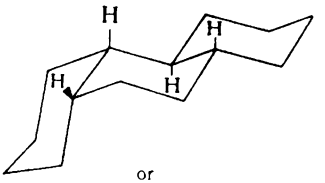


LXXII

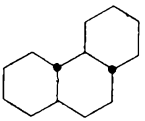
For a conventional planar representation of 10 possible stereoisomeric perhydrophenanthrenes, use is made of the following formulas and designations:



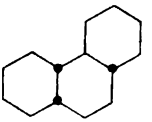

or



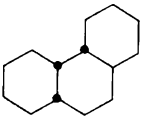

or



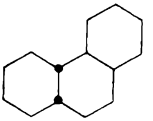
LXXIIIa *trans-anti-trans-*



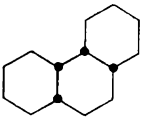
LXXIIIb *cis-anti-trans-*



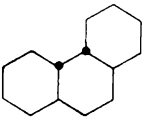
LXXIIIc, *cis-syn-trans-*



LXXIIId, *cis-anti-cis-*



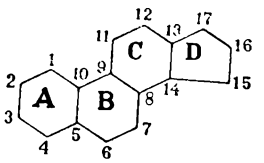
LXXIIIe, *cis-syn-cis-*



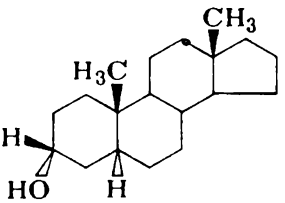
LXXIIIf, *trans-syn-trans-*

The isomers LXXIIIa through LXXIIId are chiral and therefore, aside from the structures given above, there also exist 4 optical antipodes; LXXIIIe and LXXIIIf are *meso*-forms.

The most important of the structures under consideration is **cyclopentanoperhydrophenanthrene,** which constitutes the parent ring system of an important class of natural compounds—steroids (the numbering of atoms is the one adopted at present; besides, the individual rings are designated, where necessary, by the capital letters of the Latin alphabet).



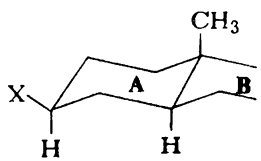
Though the structure shown is not planar (see below), it is often conventionally represented in the planar form given. The substituents may lie either below the plane of the drawing (denoted by the letter α) or above it (β). For example, in the case of 3α-hydroxy-10β,13β-dimethylcyclopentanoperhydrophenanthrene



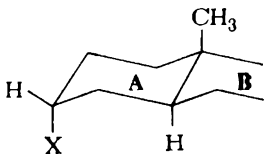

All the six junction atoms of cyclopentanoperhydrophenanthrene are asymmetric and the configuration of each of them may in principle change independently. This may give rise to $2^6$, i.e., 64 optically active antipodes of the stereoisomers due to the spatial isomerism of the cyclic structure alone. One substituent added to any of the non-junction carbon atoms doubles this number of stereoisomers.

The derivatives of perhydrocyclopentanophenanthrene, the **steroids,** apart from being biochemically important, have assumed great importance in the development of the theoretical foundations of organic chemistry and, primarily, of the basic principles of conformational analysis. This is due mainly to the fact that the cyclic system of cyclopentanoperhydrophenanthrene is rigid: no conformational mobility is possible in it. Therefore, a substituent which has a definite configuration (α- or β-) relative to the cyclic system has also a definite conformation, either equatorial or axial; its position with respect to the ring and the adjacent substituents is rigidly fixed. This allows us to see especially clearly, in the case of steroidal compounds, the effect of stereochemical factors on the stability of compounds, on the direction and rate of reactions, and on the spectral and other characteristics.

Thus, the β-substituent at C-3 in 5α-steroids occupies the equatorial position, while the α-substituent is in the axial position:




3α-

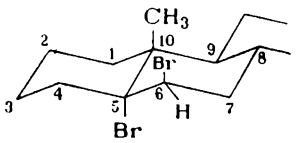



3β-

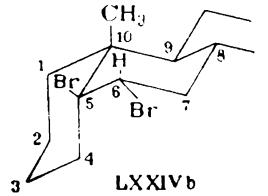
Since the equatorial position is more favourable than the axial position, 3β-isomers must be predominantly formed in thermodynamically

controlled reactions (see below the rearrangement of axial 1,2-dibromides to equatorial ones). If X is the acetoxy group (—$OCOCH_3$), its alkaline hydrolysis in the case of the equatorial orientation (in the 3β-position) will proceed faster than the hydrolysis of the axially oriented ester group. This is associated with the fact that with the axial orientation the formation of the bulky transition state required for the alkaline hydrolysis to be effected is hindered.

Steroidal compounds may be used to clearly demonstrate the validity of the rule of *trans*-elimination in reactions proceeding by the *E*2 mechanism. Such is, for example, the behaviour of two stereoisomeric dibromides LXXIVa and LXXIVb towards debromination (under the action of iodide ions):

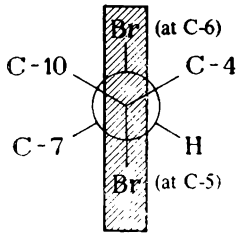



LXXIVa

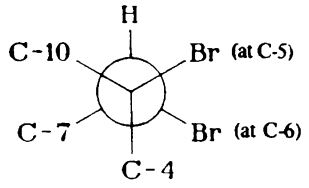



LXXIVb

The steric relationships in both stereoisomers, which are important for the reaction, can be visualized more vividly by representing the conformation along the bond between C-5 and C-6:




LXXIVa




LXXIVb

The transoid arrangement of bromine atoms required for the *E*2 elimination is possible only in compound LXXIVa which is therefore debrominated at a rate exceeding by several orders of magnitude the rate of debromination of compound LXXIVb.

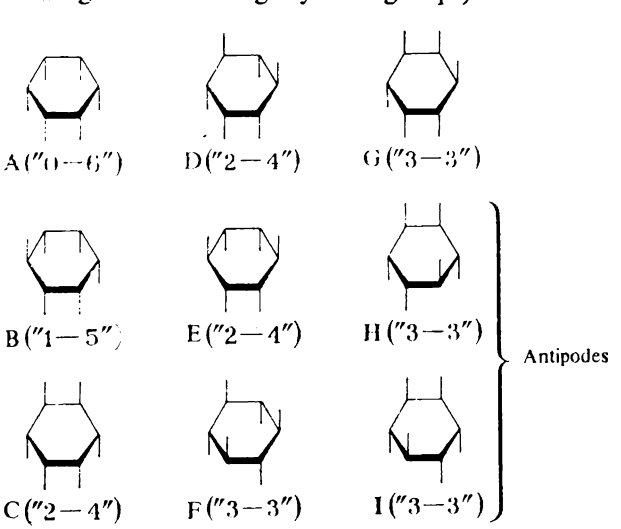
An interesting rearrangement of diaxial dibromides into diequatorial ones, which occurs on standing at room temperature, has been studied by using steroidal 1,2-dibromides.

The stereochemistry of steroids and triterpenes is an extensive independent field, the discussion of which is beyond the scope of this book. Extensive material can be found in the literature (129).

## 5.9. INOSITOL AND RELATED COMPOUNDS

**Inositol** is the hexahydric cyclic alcohol hexahydroxycyclohexane. Four isomers have been found in nature: two optically inactive forms and a pair of antipodes. But the examination of its formula suggests the existence of 8 geometrical isomers.

The number of isomers can be deduced in the same way as it is done for mono-, di- and trisubstituted benzenes. It may be assumed in this case that the substituents are those OH groups which are on the opposite side of the ring with respect to most of the OH groups. For molecules of the types "0—6" and "1—5", which correspond to unsubstituted benzene and a monosubstituted benzene, there may exist only one isomer. A "2—4" molecule corresponds to a disubstituted benzene and has three isomers corresponding to the *ortho-*, *meta-*, and *para*-isomers in the benzene series. And, finally, a molecule of the "3—3" type has three more isomers corresponding to the ordinary, symmetrical and unsymmetrical trisubstituted benzenes. It appears that the *unsymmetrical* form in this case justifies its name: it has neither plane nor centre of symmetry. Therefore, this form has a non-superimposable mirror-image molecule; the formulas H and I represent these two antipodes. The remaining isomers are optically inactive but differ in their physical properties, like diastereomers or *cis-trans* isomers (the vertical lines in the formulas given below signify OH groups).




The isomerism of inositol is, so to say, intermediate between the isomerism due to the presence of an asymmetric atom and the isomerism due to molecular asymmetry. Inositol may also be regarded as a com-

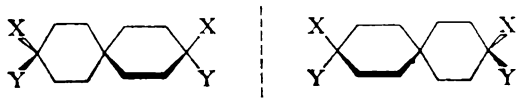
pound with six asymmetric atoms, the isomers A-G exhibiting an intramolecular compensation of asymmetric centres. Such an approach, however, would be very complicated; it is simpler to speak of the symmetry of the molecule as a whole.

It is obvious that molecular asymmetry similar to that of inositol can be displayed by all compounds of the cyclohexane series, of the general formula $C_6X_6Y_6$, say, hexachlorocyclohexane. The latter is really known to have isomers of the type in question; it has also been obtained in an optically active form (130).

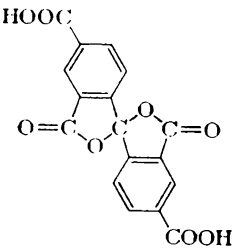
Hexachlorocyclohexane has been obtained in an optically active form by using the ability of hexachlorocyclohexanes to lose hydrogen chloride under the action of bases, as a result of which they are converted into 1,3,5-trichlorobenzene. If the optically active base brucine is used as the dehydrohalogenating agent, its action on the excess of hexachlorocyclohexane makes the dehydrochlorination of the antipodes proceed at different rates and the excess hexachlorocyclohexane left acquires an optical activity of $[\alpha]_D = +14.6°$ (in diethyl ether). The optically active form obtained is stable in acid medium; it can be, for example, recrystallized from concentrated nitric acid, but in a weakly alkaline medium there occurs rapid racemization.

## 5.10. SPIRANS

The stereoisomerism of spirans had been predicted by van't Hoff on the basis of the model of the tetrahedral carbon atom long before optically active spirans were prepared experimentally. In spirans, the two rings are locked in two mutually perpendicular planes. If the ends of this system contain different substituents, asymmetry is created:

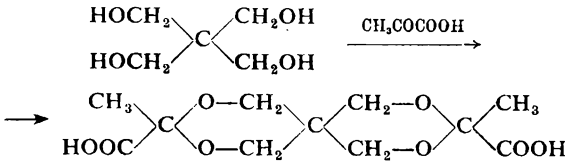



The first optically active spiran, LXXV, was described by Mills in 1920:

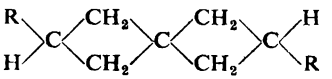



LXXV

Several years later, Böeseken condensed pentaerythritol with pyruvic acid and obtained a spiro-compound in an optically active form:

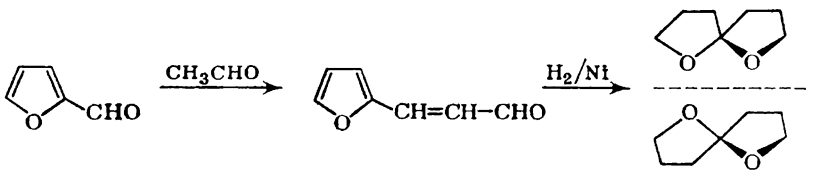


A simpler optically active spiran, LXXVI (R = COOH), was prepared by Backer in 1931:



LXXVI

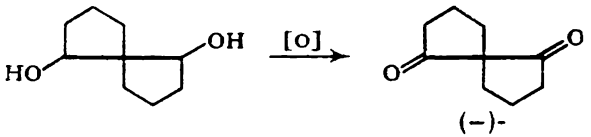
An analogous compound containing amino groups instead of carboxyl groups, LXXVI ($R = NH_2$), was obtained by Jansen and Pope in 1932. An interesting optically active spiro-compound has been prepared by Ponomarev and Zelenkova (131):



The spiro-bis-tetrahydrofuran obtained is an example of the simplest spiran asymmetric system in which the asymmetry is created by the rings themselves and not by substituents. Because of the absence of functional groups in this compound, it cannot be resolved into antipodes by ordinary methods. Ponomarev and Zelenkova prepared optically active forms of this compound by means of absolute asymmetric synthesis; the reaction was carried out on optically active quartz.

Gerlach (132) used a different approach to the preparation of an optically active spiro-compound: he prepared an optically active spirodiol by resolution into the antipodes and then oxidized it to a spiro-

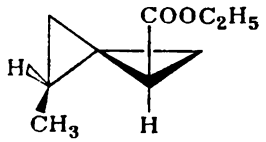
diketone [(—)-spiro-4,4-nonane-1,6-dione], in which the optical activity is due only to spiran asymmetry:



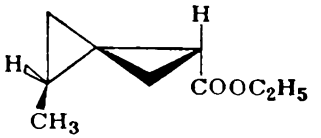

(—)-

It was precisely the configuration of the (—)-isomer shown above that was proved in this work.

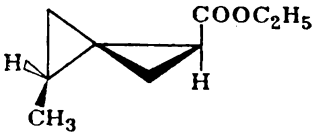
The spiro-diol, which was the intermediate in the synthesis of the optically active spiro-diketone in the work of Gerlach, is of interest in itself as an example of substituted spirans with two asymmetric carbon atoms. Compounds of such a structure may have 4 diastereomers, each of which is a racemate which can, in principle, be resolved into optical antipodes. A compound of similar structure is, for example, 1-carbethoxy-4-methylspiropentane (134):



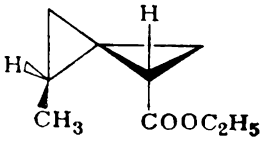

*anti*-Medium isomer




*syn*-Medium isomer

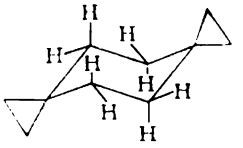



Distant isomer



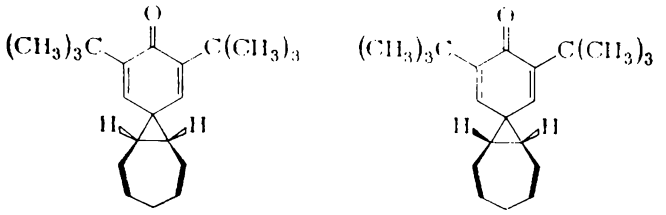

Proximate isomer

An interesting specific feature of a dispiro-compound of structure LXXVII is a high energy barrier to the conversion of the chair conformation (about 50 kJ/mole). The PMR spectra show also unusually large differences in chemical shift between the equatorial and axial protons.




LXXVII

The spiro-compound LXXVIII is of interest since it exists as two isomers which can be interconverted thermally or photochemically (135):

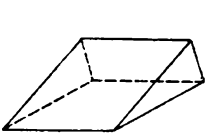


*cis-* *trans-*

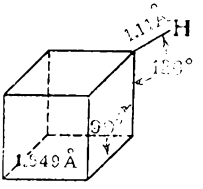
LXXVIII

## 5.11. FRAMEWORK (BRIDGED-RING) STRUCTURES

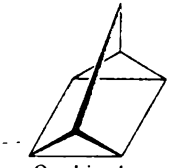
Of considerable interest are bulky polycyclic structures which are termed **bridged-ring** systems (for a review, see ref. 136).



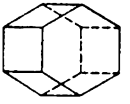
Prismane



Cubane

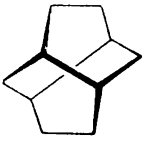


Quadricyclene
(this is norbornane
with extra bridges)

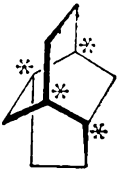


Tetrasterane

**Twistane** is a structure which may be represented as cyclohexane in the twist-boat form with two additional dimethylene bridges:

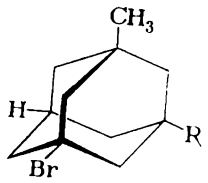


or in a different projection



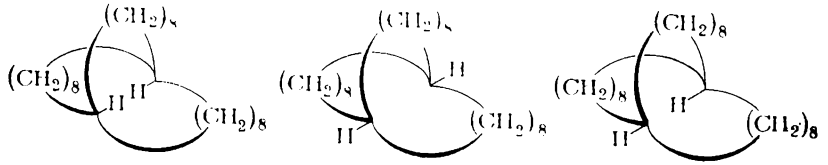
Twistane has been prepared in an optically active form. The configuration represented by the above formula was originally assigned, according to ORD data, to the (+)-antipode (137), but in 1972 it was conclusively proved, by means of a reliable chemical correlation (138), that this configuration must belong to the (—)-isomer. After the approach to the interpretation of ORD and CD data had been revised, these methods too enabled a correct estimation of the configuration of twistane (139). In twistane, strictly speaking, there are four asymmetric carbon atoms (they are marked in the formula), but the consideration of the asymmetry of the molecule as a whole is more spectacular.

Molecular asymmetry of the same type is exhibited by the derivatives of adamantane (140), a bridged-ring hydrocarbon having the diamond crystal lattice (i.e., with undistorted tetrahedral angles).




Four different substituents (H, $CH_3$, Br and R = COOH, $CONH_2$, CN) are situated at the corners of the tetrahedron but they are linked not to the central atom (as is the case in ordinary compounds with a centre of asymmetry) but to *different* carbon atoms of the bridged-ring adamantane system (212).

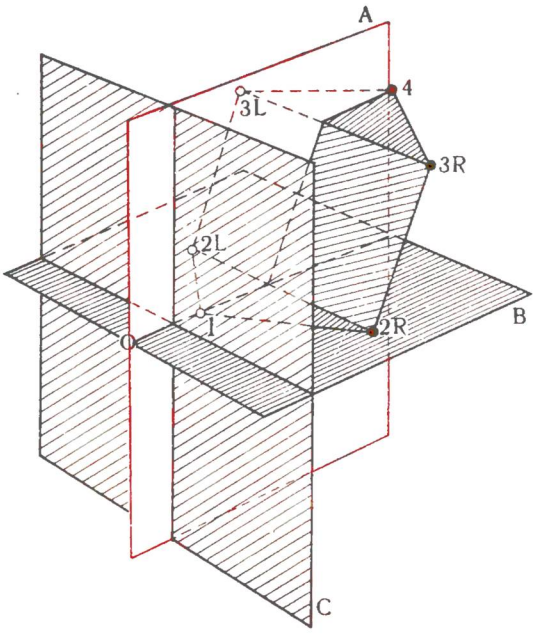
Interesting features have been detected in bicyclo[8.8.8] hexacosan, a compound with three 18-membered rings (141). This compound may exist in three stereoisomeric forms which differ in the position of hydrogens at the common carbon atoms (this type of stereoisomerism is called **out-in isomerism**):




## 5.12. THE OCTANT RULE

The accumulation of factual material together with the theoretical analysis of symmetry conditions in chromophores of different types

Figure 5.10.



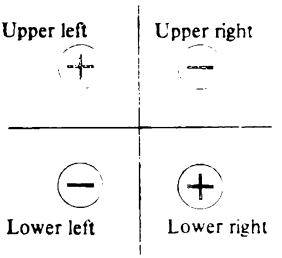

*The octant rule.*

made it possible to work out a number of rules which relate the character of ORD curves (the sign of the Cotton effect) to the configuration. Most of these rules refer to cyclic compounds. As an example, let us consider the octant rule.

The **octant rule** (214) enables us to determine the configuration of cyclohexanones (including the configurations of complex polycyclic cyclohexanones) from the sign of their Cotton effect with account taken of the conformation in which the compound exists. Cyclohexanone is pictured in a system of three mutually perpendicular planes as shown in Fig. 5.10.

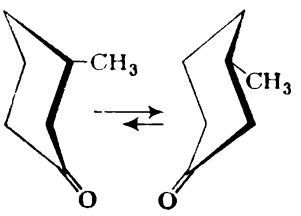
The vertical plane *A* is the plane of symmetry of cyclohexane, which passes through the carbonyl carbon and opposes the atom C-4. Two carbon atoms (the left C-2 and the left C-3 designated as 2L and 3L in Fig. 5.10) lie to the left of the plane *A*; the other two carbon atoms (the right C-2 and the right C-3; 2R and 3R) lie to the right of that plane.

The plane *B* passes through the carbonyl group and the carbon atoms adjacent to it (2L and 2R). Thus, three carbon atoms of cyclohexane lie in the plane *B* and the other three, above this plane [these are the atoms 3L, 3R and 4 (C-4)]. The plane *C* is drawn between the oxygen and the carbonyl carbon atom. The planes *A*, *B*, and *C* divide space into 8 octants. The *near octants* that lie in front of the plane *C* are vacant in the case of monocyclic cyclohexanones: all the atoms are contained in the *far octants*. Depending on the octant in which the substituent is situated, the sign of its contribution to rotation is changed. For the far octants (which are also called the back or rear octants) the signs are as follows:

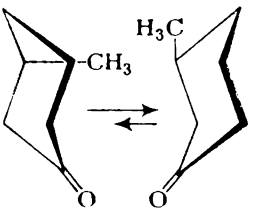



In those rare cases where substituents are found in the near (or front) octants, the signs of their contributions are reversed.

Let us consider the application of the octant rule to the determination of the configuration of the simplest compound of this type—3-methylcyclohexanone. It exists as a pair of antipodes, each of which may in principle have two conformations:

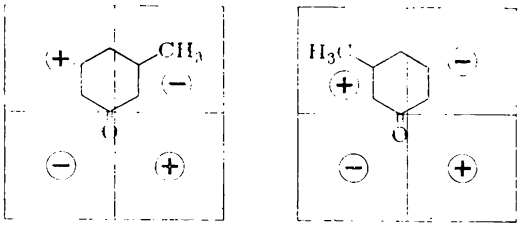



LXXIX a




LXXIX b

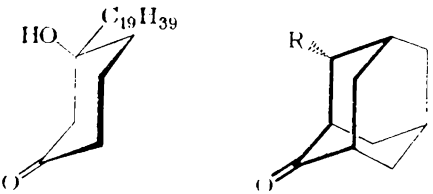
Based on general conformational considerations, we must of course give preference to conformations with an equatorial methyl group (these conformations are given on the right in both cases). Suppose that we have (+)-3-methylcyclohexanone at our disposal, which has a positive Cotton effect. What configuration must it have according to the octant rule?



LXXIXa LXXIXb

In stereoisomer LXXIXa, the substituent lies in the upper right octant: with this arrangement a negative Cotton effect must be observed. The stereoisomer LXXIXb must, accordingly, have the positive sign of the Cotton effect: hence, this is our (+)-3-methylcyclohexanone. We have just considered only the simplest example—the configuration of 3-methylcyclohexanone had been known long before the spectropolarimetric method was devised. In many other cases, however, the octant rule has been used to advantage in configurational studies.

Thus, for example, the octant rule has been used to determine the conformation of hydroxyketone (+)-LXXX, the hydrogenation product of a natural unsaturated keto alcohol (215).



LXXX LXXXI

In those cases where the configuration is known, the use of the octant rule allows us to determine the conformation. Examples illustrating the use of the octant rule for this purpose will be discussed at a later time.

Snatzke and Eckhardt (144) employed the octant rule for analysis of the circular dichroism of adamantane ketones LXXXI. The meaning of these investigations consists in that adamantanones contain a cyclohexane fragment in the rigidly fixed chair conformation (this fragment is marked by heavy lines in formula LXXXI). The substituents may be either strictly axial or strictly equatorial. Thus, compounds of the type LXXXI may serve as models for the testing of the octant rule. The data obtained show that the octant rule is observed here only for equa-

torial R (except for R = fluorine); with axial substituents the sign of the Cotton effect is opposite to that required by the octant rule.

Snatzke developed a generalized approach to the consideration of the sign of the Cotton effect for various compounds with a ketonic chromophore, in particular, α,β- and β,γ-unsaturated ketones (145) and also tetralones (146). It has been suggested that the octant rule be also used for azide chromophore (147).

The octant rule is only an example of a large number of empirical and semi-empirical regularities which relate the conformation and configuration of optically active compounds to the signs of the Cotton effect characteristic of them. Thus, Klyne and coworkers (148) proposed the sector rule for lactones. The works of Japanese authors are devoted to the rules for determination of the configuration of cyclic alcohols and glycols from the sign of the Cotton effect of their benzoates (149). Ripperger (150) suggested the quadrant rule for the determination of the sign of the Cotton effect for the dithiourethanes of optically active amines.

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CHAPTER 6

# Stereochemistry of Compounds with Multiple Carbon-Carbon Bonds

## 6.1. PHYSICAL PROPERTIES OF CIS-TRANS ISOMERIC ACYCLIC OLEFINS AND THEIR USE FOR CONFIGURATION DETERMINATIONS

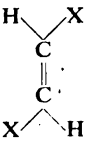
The geometrical (*cis-trans*) isomerism of cyclic compounds has been discussed in detail in the preceding chapter. If certain structural conditions are fulfilled, this type of spatial isomerism occurs also in ethylenic compounds, in which, as a matter of fact, it was first discovered and studied on the well-known example of fumaric and maleic acids.

Each of the geometrical isomers is characterized by its own physicochemical properties. The difference in properties between *cis-* and *trans-*forms is often no less than between structural isomers. In the majority of cases, certain regularities may be traced out in these differences. This enables us to use physical methods for the determination of the configurations of *cis-trans*-isomeric forms.

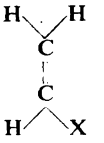
### 6.1.1. DIPOLE MOMENTS

Many *cis-trans* isomers may display characteristic differences in the magnitude of dipole moments (1). In compounds of the type XCH=CHX,

where X is a single atom or a simple group with cylindrical symmetry, the dipole moment of the *trans*-form is equal to zero:

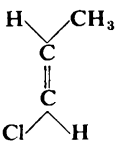


$\mu = 0$

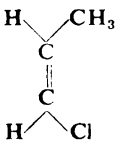


| X | $\mu$, D |
|---|---|
| F | 2.42 |
| Cl | 1.89 |
| Br | 1.35 |
| I | 0.75 |

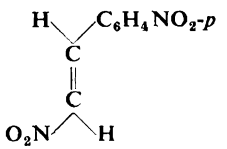
If there are different substituents at the double bond, the dipole moment of the *trans*-form will naturally not be equal to zero, but the differences for the *cis-trans* isomers of such compounds are in many cases sufficiently characteristic:



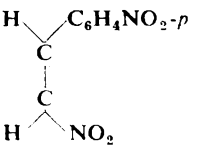
$\mu = 1.97$ D



$\mu = 1.71$ D



$\mu = 0.50$ D



$\mu = 7.38$ D

In the case of 1-chloro-1-propene the dipole moment of the *trans*-form is *greater* than that of the *cis*-form since the methyl group has electron-donor and the chlorine atom electron-acceptor properties, and with the *trans*-configuration there takes place the vectorial addition (and not subtraction as in the other examples given above) of the dipole moments of both polar bonds. This example must warn of the occasionally arising erroneous view that the *cis*-form must have a high dipole moment *in all cases*.

If there are more complex substituents at the double bond, which are capable of rotating freely and forming a number of conformations, the differences between the dipole moments of the geometrical isomers

become non-characteristic. Examples of such compounds are diethyl esters of maleic and fumaric acids with the dipole moments equal to 2.54 and 2.38 D, respectively, and also the *cis*- and *trans*-2-butene-1,4-diols with the dipole moments 2.48 and 2.45 D.

### 6.1.2. INFRARED AND RAMAN SPECTRA

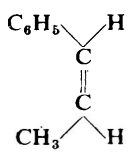
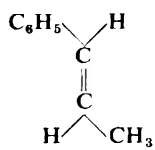
The infrared spectra of the *cis-trans* isomers of unsymmetrically substituted ethylenes of the type R—CH=CH—R′ show characteristic differences:

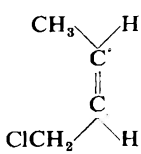
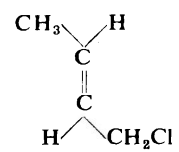
| | *cis*-Isomer | *trans*-Isomer |
|---|---|---|
| Stretching vibrations of C=C | 1660 (medium) | 1675 (weak) |
| Deformation vibrations of C—H | 730-675 (strong) | 965 (strong) |

The vibration band of C=C for *cis*-forms is more intense than that for *trans*-forms.

In the *trans*-isomers of symmetrically substituted olefins, the stretching vibrations of the C=C bond produce no change in the dipole moment of the molecule (i.e., the dipole moment remains to be equal to zero), and therefore there is no absorption band in the rigion of 1600 $cm^{-1}$ in the IR spectra of such compounds. For example, in the case of 1,2-dichloroethylene only the *cis*-form exhibits strong absorption at 1590 $cm^{-1}$ in the IR spectrum.

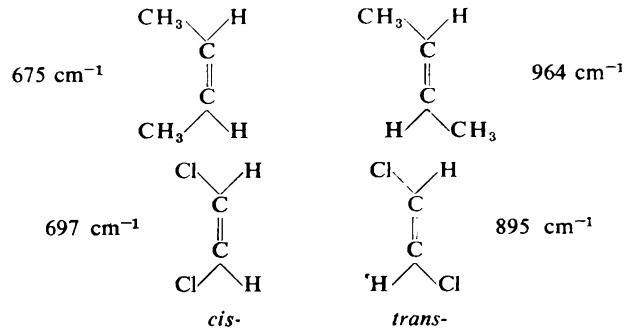
The differences in the Raman spectra of *cis-trans* isomers are reminiscent of the analogous differences in the IR spectra: in *cis*-olefins the band of stretching vibrations of the carbon-carbon double bond is at lower frequencies (1654-1657 $cm^{-1}$) than that in *trans*-olefins (1668-1671 $cm^{-1}$). For example,

1653 $cm^{-1}$  1667 $cm^{-1}$ 

1660 $cm^{-1}$  1675 $cm^{-1}$ 

*cis-* *trans-*

Another criterion is the out-of-plane vibrations of the C—H bond in the region of 690 $cm^{-1}$ for *cis*-isomers and in the region of 970 $cm^{-1}$ for *trans*-isomers:

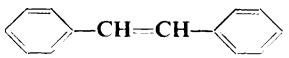



*cis*-Isomers sometimes also exhibit a band of about 900 $cm^{-1}$ but the intensity of this band is low ($\varepsilon$ is about 20 instead of 150 for frequencies in the region of 970 $cm^{-1}$ for *trans*-isomers).

In the case of trisubstituted olefins of the type XYC=CHZ the differences in the IR spectra of *cis-trans* isomers are less marked, though in a number of cases their IR spectra too have been successfully used for configuration determinations, for example, for the elucidation of the *cis*-configuration of the double bond in the side chain of jasmone. The spectra also provide information on finer details of the structure of unsaturated compounds. Thus, Raman spectra have enabled the planar structure of perfluoropropylene to be confirmed (2) contrary to the existing interpretation of the older electron diffraction data indicating the distortion of the double bond.

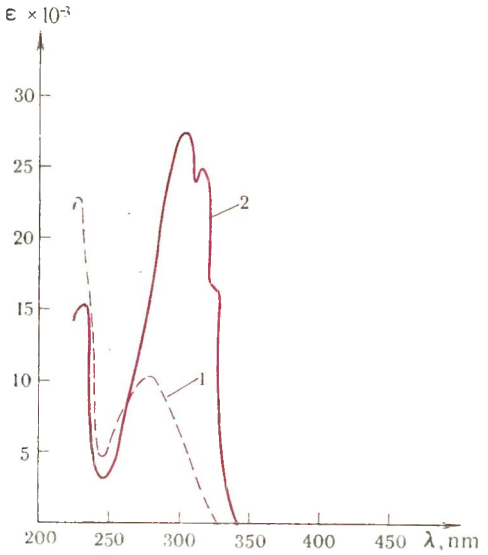
### 6.1.3. ULTRAVIOLET SPECTRA

The ultraviolet spectra of the *cis-trans* isomers of unsaturated compounds show characteristic differences in many cases. This especially refers to compounds of the stilbene (diphenylethylene) type (3).



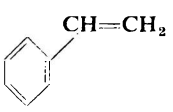
The benzene rings and the ethylenic double bond of stilbene form a single conjugated system. If nothing prevents the conjugation, the UV spectra will show an increased intensity of the absorption band of the aromatic nucleus and its shift to the longer-wavelength region. The conjugation requires that the $\pi$-systems of the benzene rings and the double bond be arranged in the same plane, i.e., that the molecule be coplanar. But this is possible only in the *trans*-form: in *cis*-

Figure 6.1.

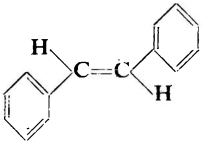



*The ultraviolet (UV) spectra of cis- (curve 1) and trans-isomers (curve 2) of stilbene.*

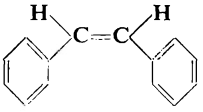
stilbene, the benzene rings interfere with each other and cannot be arranged in the same plane:




Styrene
$\lambda_{max}$ = 282-292 nm
(ε = 6000)



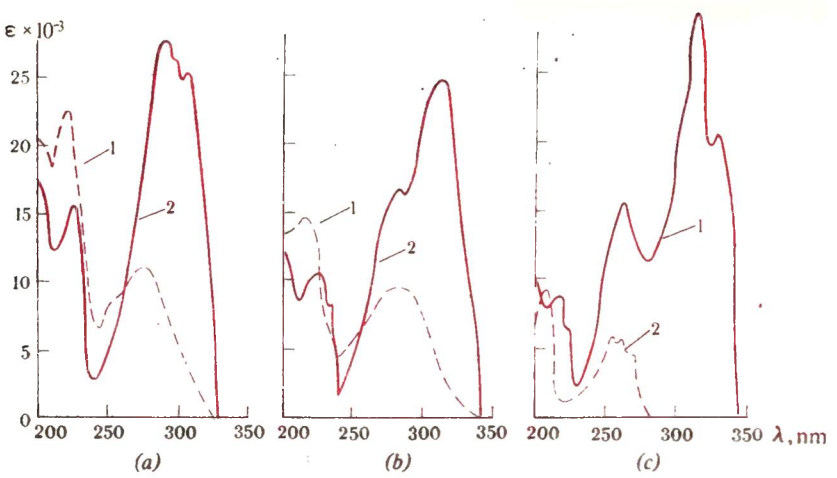

*trans*-Stilbene
$\lambda_{max}$ = 296 nm
(ε = 29,000)




*cis*-Stilbene
$\lambda_{max}$ = 280 nm
(ε = 10,500)

Compounds of the stilbene series were the subject of investigations carried out, in particular, by the Dutch chemist Havinga. In one of his works, Havinga studied the effect of *para*-substituents in the stilbene molecule on the character of the UV spectra of the compounds (4). Figure 6.1 shows the UV spectra of the *cis*- and *trans*-isomers of unsubstituted stilbene. When substituents, the free-electron pairs or π-bonds of which may enter into conjugation with the benzene rings, are introduced into the *para*-position, the absorption maxima shift to the

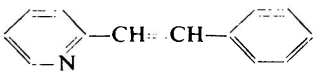
Figure 6.2.



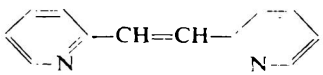

*The UV spectra of cis- (curve 1) and trans-forms (curve 2) of stilbene (a), α-stilbazole (b), and α-pyridostilbene (c).*

longer-wavelength region. When substituents are introduced into the *ortho*-position of the benzene rings or to the ethylenic carbon atoms, steric hindrances to conjugation arise in the *trans*-form too: this is detected by the shift of the UV-absorption maximum to the shorter-wavelength region and by the fall of its intensity (5). The calculated data indicate that in stilbenes with *ortho*-substituents, which create steric hindrances, the benzene rings may be turned at an angle of up to 50° (6).

An analogous use has been made of UV spectra for the determination of the configuration of the heterocyclic analogues of stilbene, for example, of α-pyridostilbene I and α-stilbazole II.




I




II

α-Stilbazole has long been known as a solid compound with m.p. 91°C. While studying the by-products of the synthesis of stilbazole, Katsumoto (7) isolated the second, liquid isomer. For the configurations of the compounds to be determined, the ultraviolet spectra of the two forms of α-stilbazole, the *cis*- and *trans*-forms of stilbene and the *cis*- and *trans*-forms of α-pyridostilbene were compared (Fig. 6.2).

The ultraviolet spectra of all the three pairs of *cis-trans* isomers are quite similar, which allows the configurations of the nitrogen analogues of stilbene, I and II, to be elucidated on the basis of the specific features of the UV spectra of its *cis-trans* isomers.

Other examples showing that a break in the conjugation in the *cis*-forms of substituted ethylenes leads to the shift of the absorption bands in the UV spectra into the shorter-wavelength region and to the decrease of the absorption intensity are presented in Table 6.1.

TABLE 6.1. THE CONSEQUENCES OF A BREAK IN THE CONJUGATION OF CHROMOPHORES IN THE UV SPECTRA OF SUBSTITUTED ETHYLENES

| Compound | Formula | For *trans*-isomer | | For *cis*-isomer | |
|---|---|---|---|---|---|
| | | $\lambda_{max}$, nm | $\varepsilon$ | $\lambda_{max}$, nm | $\varepsilon$ |
| Stilbene | $C_6H_5—CH=CH—C_6H_5$ | 295.5 | 29,000 | 280 | 10,500 |
| α-Methylstilbene | $C_6H_5—C(CH_3)=CH—C_6H_5$ | 270 | 20,000 | 260 | 11,900 |
| 1-Phenylbutadiene | $C_6H_5—CH=CH—CH=CH_2$ | 280 | 28,300 | 265 | 14,000 |
| Cinnamic acid | $CH_3—CH=CH—COOH$ | 295 | 27,000 | 280 | 13,500 |
| Dimethyl ester of fumaric acid | $CH_3OCO—C(H)=C(H)—COOCH_3$ | 214 | 34,000 | | |
| Dimethyl ester of maleic acid | $CH_3OCO—C(H)=C(H)—COOCH_3$ | | | 198 | 26,000 |

## 6.1.4. NUCLEAR MAGNETIC RESONANCE SPECTRA

The spin-spin coupling constants of the olefinic protons of the *cis-trans* isomers of disubstituted ethylenes are, as a rule, different: the spin-spin coupling constant is usually 4-12 cps (7 cps on the average) with the *cis*-arrangement of the protons at the double bond and 12-18 cps (15 cps on the average) with the *trans*-arrangement. The signals of olefinic protons lie in the region of 4-5 ppm, and not infrequently this portion of the spectrum is found to be highly saturated with signals, which makes their interpretation considerably difficult. In such cases, the procedure that has already been mentioned (see page 161) may be helpful, namely, the study of the PMR spectra in the presence of "shift reagents"—complexes of rare-earth metals. This procedure

has, for example, been used (8) for the determination of the configuration of alkenes having the structure R—CHX—CH=CH—R′, where X is a functional group capable of complex formation. Shift reagents have also been used to determine the configuration of 2-cyano-3-ethoxyacrylic acid (9).

Another method has proved to be useful in the elucidation of the configuration of compounds of the type R—CH=CR—$SO_2X$, where X = Cl or OH. The difference in the chemical shifts of olefinic protons when measured in benzene and carbon tetrachloride has been found to be associated with the configuration of the compounds (10).

### 6.1.5. OTHER PHYSICAL PROPERTIES

Most geometrical isomers show characteristic differences in melting point and solubility in various media. As a rule, the *trans*-form has a higher melting point and a lower solubility than the *cis*-form. As an example, data for α,β-unsaturated carboxylic acids are presented here (Table 6.2).

TABLE 6.2. THE MELTING POINTS AND SOLUBILITIES OF A NUMBER OF SELECTED α,β-UNSATURATED CARBOXYLIC ACIDS

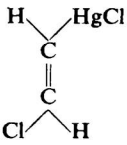
| Acid | Formula | m.p., °C | | Solubility in water, per cent | |
|---|---|---|---|---|---|
| | | *trans-* | *cis-* | *trans-* | *cis-* |
| α,β-Dibromocinnamic | $CH_3$ CBr=CBr –COOH | 120 | 94 | Difficultly soluble* | Readily soluble* |
| Cinnamic | $C_6H_5$—CH=CH—COOH | 133 | 68 | 0.0546 | 0.845 |
| α-Chlorocinnamic | $C_6H_5$—CH=CCl—COOH | 137 | 110 | 0.025 | 0.3 |
| β-Chlorocinnamic | $C_6H_5$– CCl=CH –COOH | 142 | 133 | 0.02 | 0.04 |

* Data on solubility in ligroin.

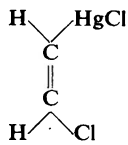
Exceptions are however known, where the higher-melting form proves to be more soluble.

Werner pointed to the well-known analogy between the *cis-trans* isomers and *ortho*- and *para*-isomers of aromatic compounds. This analogy has been used by A. N. Nesmeyanov for the determination of the configuration of the *cis-trans*-isomeric β-chlorovinylmercurichlo-

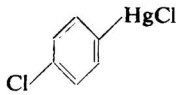
rides through the comparison with the related compounds of the benzene series:



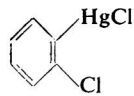
III, m.p. 124°C



IV, m.p. 79°C



V, m.p. 225°C



VI, m.p. 145°C

The high-melting isomer of β-chlorovinylmercurichloride, III, is similar to *p*-chlorophenylmercurichloride V, which allows us to assign the *trans*-structure to it.

The *cis-trans* configuration can sometimes be determined from the difference in dissociation constants as well. Let us examine the regularities observed in such cases, using fumaric and maleic acids as examples:

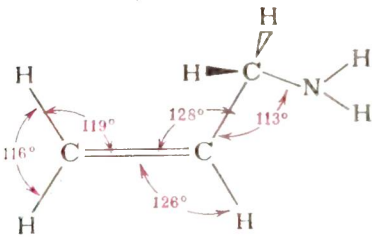
| | Maleic acid (*cis*-) | Fumaric acid (*trans*-) |
|---|---|---|
| Dissociation constant | | |
| first | $1.2\times10^{-2}$ | $1\times10^{-3}$ |
| second | $3\times10^{-7}$ | $3\times10^{-5}$ |

Because of the spatial proximity of the two carboxyl groups in the *cis*-form the tendency of the hydrogen atom to ionize is enhanced, and therefore the first dissociation constant of maleic acid is higher than the first constant of fumaric acid. It is however difficult for the second proton to overcome the attraction of the two closely spaced $COO^-$ groups in the *cis*-form, for which reason the second dissociation constant of maleic acid is lower than that of fumaric acid.

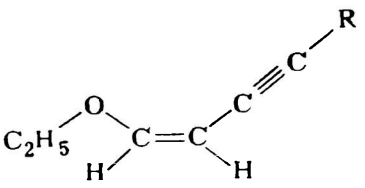
Having higher symmetry, the *trans*-forms are thermodynamically more stable than the *cis*-forms. This is reflected, for example, in the fact that the heat of combustion of maleic acid as the *cis*-isomer is higher (1370 kJ/mole) than the heat of combustion of the *trans*-isomer of fumaric acid (1340 kJ/mole). The difference in energy content also manifests

itself in that the *cis*-forms may often spontaneously turn into the energetically more favourable *trans*-forms; the reverse conversion is possible only when a certain quantity of energy is consumed, say, in the form of ultraviolet radiation.

The conformations of unsaturated compounds have also been studied. For instance, the conformation VII has been found, according to calculated data, to be the most favourable for allylamine (11).




VII




VIII

Based on dipole moment measurements, the conformation of ethynylvinyl esters VIII has been determined (12).

There have also been determined the energy barriers to rotation for substituents adjacent to the double bond: for methyl groups this barrier is 8-10 kJ/mole (13), i.e., it is significantly lower than in ethane (see page 222).

## 6.2. STABILITY AND INTERCONVERSIONS OF CIS-TRANS ISOMERIC ACYCLIC OLEFINS

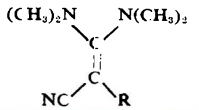
Geometrically isomeric forms, the difference between which is associated with the arrangement of substituents about the double bond, i.e., *cis-trans* isomers, differ from stereoisomeric forms of a different type—conformers (the difference between which is due to the different disposition of substituents about a single bond) basically in that the energy barrier between *cis* and *trans* isomers is sufficiently high to provide a separate existence of the two spatial forms, whereas the conformers exist only in the form of an equilibrium mixture because of the low energy barriers separating them.

The height of the barrier to rotation about the double bond in simple alkenes (ethylene, 2-butene) amounts to 250-270 kJ/mole (14). If the double bond is adjacent to functional groups that cause the polarization of the double bond or make it a part of the conjugated system, the barrier to rotation decreases. This has been observed, for example, for ethylenic compounds of the type ABC=CXY, where A and B are

electron-donors (say, the —SR groups) and XY are electron-acceptors (—CN, —$COC_6H_5$). The barrier to rotation about the thus polarized bond falls down to 60-100 kJ/mole (15). The barriers to rotation (expressed in $\Delta G^{\neq}$) about bonds in conjugated systems are given in Table 6.3 [based on the data obtained by Kessler (16)].

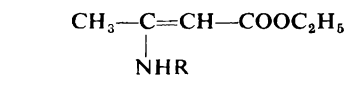
The figures listed in Table 6.3 show that both types of barriers can really be equilibrated: with R = $COOC_2H_5$, for example, the energy differences between the *cis-trans* isomers and conformers are smoothed out.

TABLE 6.3. ROTATIONAL BARRIERS IN CONJUGATED SYSTEMS OF THE TYPE

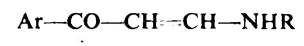


| R | $\Delta G^{\neq}$ (kJ/mole) about bonds | | | |
|---|---|---|---|---|
| | C=C | (a) C—N | (b) C—N | C—R |
| $COOC_2H_5$ | 56.6 | 58.3 | — | — |
| $C_6H_5$ | 88.0 | 48.7 | 50.7 | 41.9 |
| $C_6H_4Cl$-*p* | 34.2 | 49.6 | 51.6 | 41.9 |
| $C_6H_4OCH_3$-*p* | 74.7 | 54.1 | 55.2 | 43.2 |

The low barriers to the interconversion of *cis-trans* isomers have also been observed for amino derivatives of acetoacetic esters IX and enamine ketones X:



IX



X

It has been shown (17), with the aid of two independent methods (NMR and ORD), that the position of equilibrium in such systems depends on the nature of the solvent. Thus, for example, enamine ketones X in non-polar solvents exist by 100 per cent in the *cis*-form stabilized by the intramolecular hydrogen bond; in polar solvents, up to 50 per cent of the *trans*-form appears.

It is well known that maleic acid on heating or in the presence of catalysts isomerizes to fumaric acid; thus, in this pair, the *trans*-isomer is found to be the more stable. The same situation is observed in the

case of cinnamic acids, stilbenes, 2-butenes and many other compounds. One cannot, however, generalize this fact and state that *trans*-forms are always *invariably* more stable than *cis*- forms.

This may be illustrated by the following data. While studying the mixed halogen derivatives of ethylene, Viehe obtained 1-bromo-2-fluoroethylene and separated it into two isomers with melting points 20 and 30°C. The isomer with a higher melting point has a greater refractive index and a higher density, which allows us (on the basis of the well-known Auwers-Skita rule) to assign the *cis*-structure to it. This is confirmed by the character of its IR spectrum and also by the measurement of the dipole moment which amounts to 1.9 D against 0.3 D for the isomer with a lower melting point, which is the *trans*-form. If both isomers are heated with acids at 100°C, there will be obtained an equilibrium mixture consisting predominantly of the *cis*-isomer (75 per cent); this indicates that in this case the *cis*-isomer is thermodynamically more stable (18).

Having detected such a deviation from the rule, Viehe studied this phenomenon more thoroughly. In particular, he found a number of other examples in the literature, showing that *cis*-isomers are more stable. It has been established that of 1,2-dihalogenoethylenes only the *trans*-form of 1,2-diiodoethylene is more stable than the *cis*-form, whereas in the case of 1,2-dibromoethylene the *cis*-form is by 0.7 kJ/mole more favourable energetically than the *trans*-form. The same is observed for 1-bromo-1-propene: the equilibrium mixture consists of 80 per cent of the *cis*-form and the free energy difference is about 2 kJ/mole in favour of the *cis*-form. Similar values have been obtained for 1,2-dichloroethylene and for a number of other substituted ethylenes (19), such as 1-chloro-2-iodoethylene, 1-bromo-2-iodoethylene.

In this connection, it will be recalled that in discussing the data on the conformation of dihaloethanes or monohalopropanes (see page 231) we were convinced that in a number of cases the skew form with closely spaced substituents is more stable than the transoid form. Thus, we have to admit again that not only the repulsive but also the attractive forces are operating between the substituents, including similar substituents. While discussing these data (20), Viehe came to the conclusion that the attractive forces (of the London forces type) usually predominate between substituents provided only that there is no pure non-bonded H—H interaction (hydrocarbons) or the substituent is not too bulky (1,2-diiodoethylene, stilbene, fumaric and maleic acids).

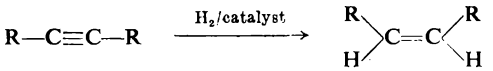
## 6.3. PREPARATION OF CIS-TRANS ISOMERS

Taking advantage of the differences in physical properties between *cis* and *trans* isomers, their mixtures can be separated into the individual

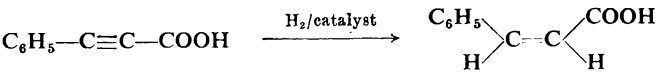
isomers by using such methods as distillation, crystallization, chromatographic techniques. Since these operations are quite identical with the conventional operations used to separate mixtures of organic compounds, there is no need to consider them in more detail. Of more interest here are the reactions of formation of double bonds, in which a certain definite stereoisomer is predominantly formed. These reactions are primarily the hydrogenation of acetylenic hydrocarbons, elimination reactions with the formation of a double bond.

### 6.3.1. ADDITIONS TO TRIPLE BONDS

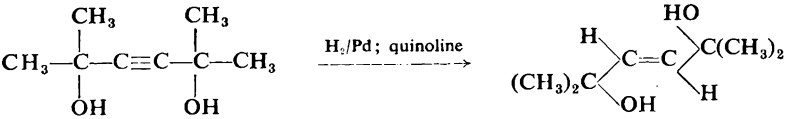
The catalytic hydrogenation of acetylenes gives predominantly (80-95 per cent) *cis*-isomers. The cause is obvious: both hydrogen atoms approach the double bond from the same side—from the side of the catalyst.



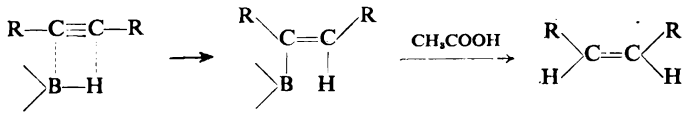

As an example may be cited the hydrogenation of phenylpropiolic acid:



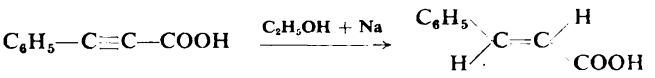

Many other examples could be cited here. One of the few exceptions is the hydrogenation of tetramethylbutynediol over palladium in the presence of quinoline:




*cis*-Olefins are also formed on hydroboration, which evidently proceeds according to the scheme:

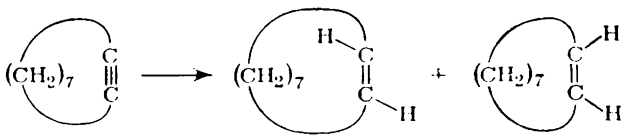


The reduction with nascent hydrogen (sodium in alcohol, zinc in acetic acid) leads, as a rule, to thermodynamically more stable forms, more often, to *trans*-isomers; for example:




It will be recalled that the catalytic hydrogenation of the same phenylpropiolic acid gives *cis*-cinnamic acid. Thus, by adding hydrogen under various conditions, one can eventually obtain the desired isomers. The analogous dependence of the stereochemical result on the reaction conditions has also been observed in many other cases.

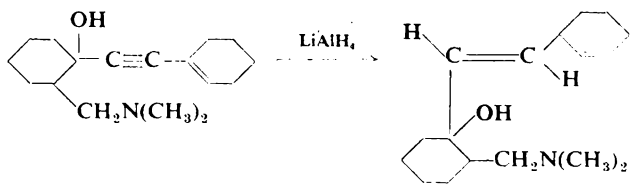
The reduction with nascent hydrogen (sodium in alcohol) yields *trans*-olefins even in those cases where they are thermodynamically less stable; for example,




Cyclononyne — *trans*-Cyclononene 79% + *cis*-Cyclononene 21%

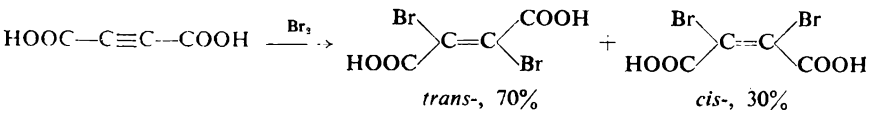
This is evidence that the reaction is governed by stereoelectronic rather than thermodynamic factors (21).

*trans*-Isomers are also formed upon reduction of acetylenic alcohols with lithium aluminium hydride; for example,



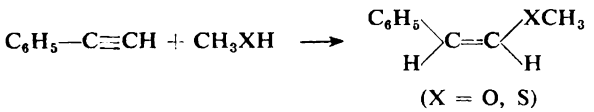

The conversion of acetylenic into ethylenic compounds is possible not only by way of hydrogenation; other reagents, such as halogens and halogen acids, can also add to the triple bond. It is these reac-

tions that were studied as early as the last century. In his classical works, Michael studied, in particular, acetylenedicarboxylic acid and its esters. The addition of bromine leads to the predominant formation of the *trans*-isomer:

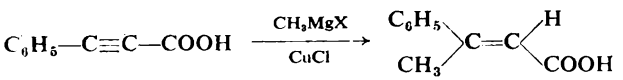


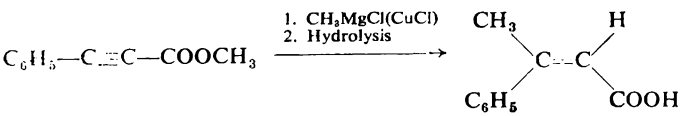

Smirnov-Zamkov and Shilov (22) carried out a detailed study of the steric direction of the addition of hydrogen bromide to an ester of acetylenedicarboxylic acid. Depending on the conditions (solvent, temperature, addition of salts), there was observed a change in the ratio of the amounts of the geometrical isomers formed—the esters of bromofumaric and bromomaleic acids. The reaction when conducted in benzene gives more than 90 per cent of the *trans*-form.

The nucleophilic addition of the anions $CH_3O^-$, $RS^-$, $ArS^-$ also proceeds by the *trans*-scheme:



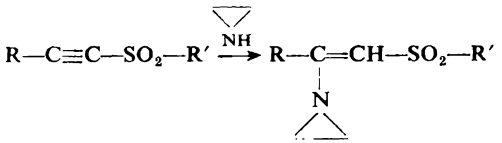

The action of organomagnesium compounds on acids of the type R—C≡C—COOH and their esters gives not only the corresponding acetylenic alcohols as the result of the reaction across the carbonyl group but the products of addition to the triple bond can also be isolated (especially in the presence of cuprous chloride). In this case, the steric course of the reaction is found to be different for acids and their esters (23):




6.3. Preparation of Cis-Trans Isomers

The addition of ethylenimine to acetylenic sulphones and sulphoxides proceeds non-stereospecifically (24):



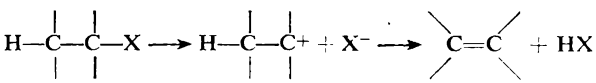
A mixture of *cis*- and *trans*-

### 6.3.2. 1,2-ELIMINATION REACTIONS

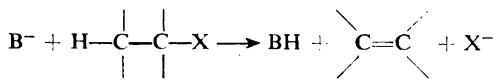
The factual material on the stereochemical specificity of elimination reactions leading to the formation of double bonds began accumulating as early as the end of the last century: it became known that diastereomers enter into these reactions at different velocities and give different reaction products. The theoretical aspect of the problem, however, was clarified only in the forties of this century simultaneously with the elaboration of mechanisms of the principal types of organic reactions by English investigators, the leading scientist among whom was later Ingold. The initial stage of development of the conceptions of the mechanisms and stereochemistry of elimination reaction has been described by Ingold (25).

According to Ingold, two principal mechanisms of heterolytic 1,2-eliminations are distinguished:

1. The **unimolecular mechanism** (*E*1) in which the electron-attracting group X breaks away, taking its previously shared electrons; the second stage (which is more rapid and therefore does not determine the rate of the overall reaction) is the expulsion of a proton from the β-position:

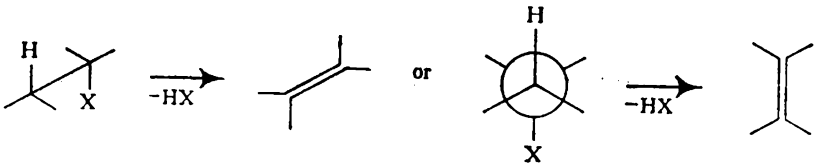


2. The **bimolecular mechanism** (*E*2) in which a base B extracts the protonic part of a combined hydrogen atom, while an electron-attracting group X simultaneously separates in possession of its previously shared electrons:



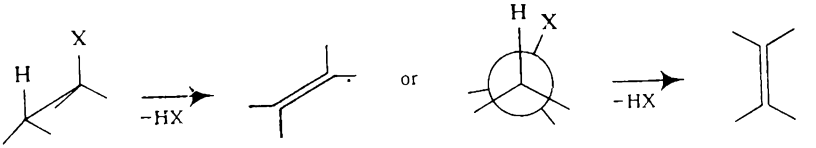
The unimolecular elimination is non-stereospecific in most cases, whereas in the bimolecular elimination reaction an important part is played by steric factors. These manifest themselves in the form of **stereoelectronic requirements**—the necessity of a definite spatial orientation of the electronic orbitals involved in the elimination. The heterolytic 1,2-elimination reaction by the *E*2 mechanism most often takes place in the case of the transoid arrangement of the groups participating in the reaction. Below are given the two representations of the corre-

sponding scheme — with the use of perspective (sawhorse) and Newman projection formulas:

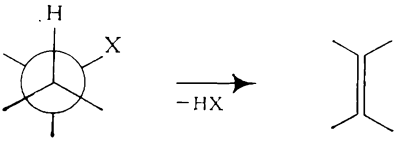



Apart from the term *transoid* elimination, use is also made of the terms *trans*-elimination and *anti*-elimination. Reactions such as the elimination of halogens, halogen acids, water, amines, etc., usually proceed by the scheme of transoid elimination.

Bimolecular elimination reactions may also occur with the cisoid orientation of the groups to be eliminated:




Apart from the name *cisoid* elimination, the terms *cis*-elimination and *syn*-elimination are also used in the literature. Instead of the eclipsed conformation, the energetically more favourable skew conformation is also assumed for the cisoid elimination:




Direct experimental evidence for the transoid elimination in *E*2 reactions has been obtained for deuterated 2-bromobutane (the deuterium atom is in position 3) (26). The investigation was carried out with pure diastereomers having the *erythro*- and *threo*-configurations. Four reaction conformations can be predicted, each of which leads to the formation of a reaction product characteristic of it. Let us consider these four pathways, using the *erythro*-isomer as an example (see the upper scheme on page 420).

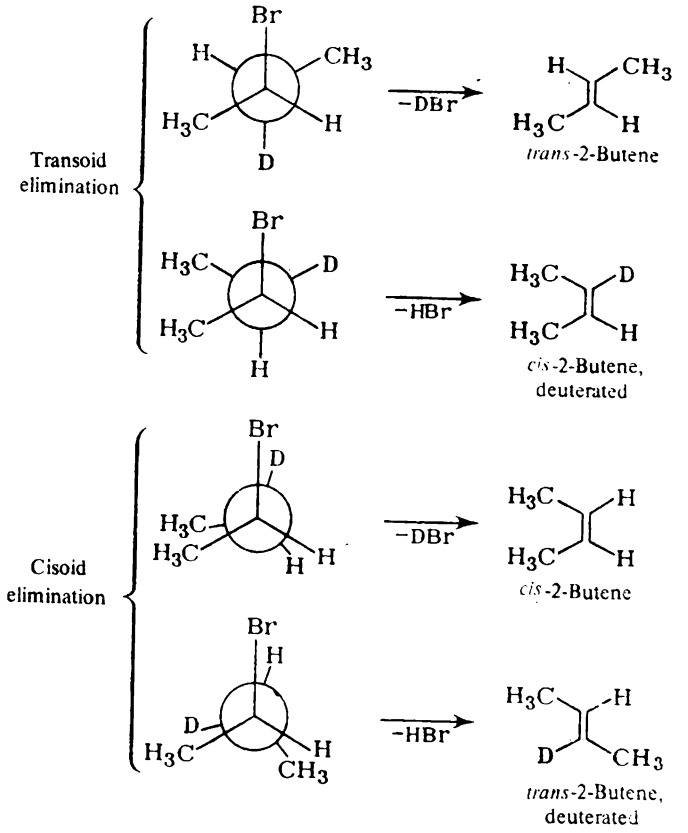
The fact that the reaction gives *trans*-2-butene containing *no* deuterium and *deuterated cis*-2-butene is evidence that the reaction proceeds

by the scheme of transoid elimination. These results were confirmed later (27).

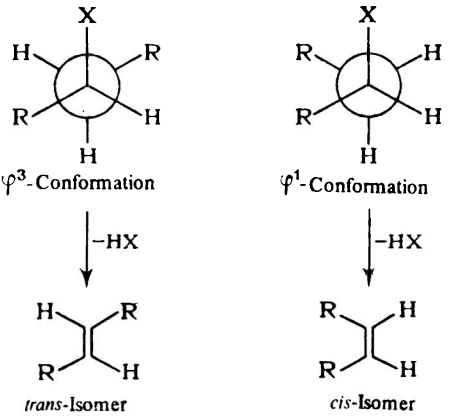
As can easily be understood, the creation of the required reaction conformation depends on the nature of the substituents present in the starting material. Depending on the volume and electronic properties of the substituents, their ability to form hydrogen bonds and other factors, the conformation required for the reaction may be either favourable or unfavourable, it can be built easily or difficultly, and this in its turn determines the ease with which the reaction takes place, its velocity, and, in certain cases, its direction too. It is in such cases that **steric factors** (steric requirements) come into play in 1,2-eliminations.

$CH_3-CHBr-CHD-CH_3$

Deuterated 2-bromobutane



The elimination from compounds of the type $R—CH_2—CHX—R$:



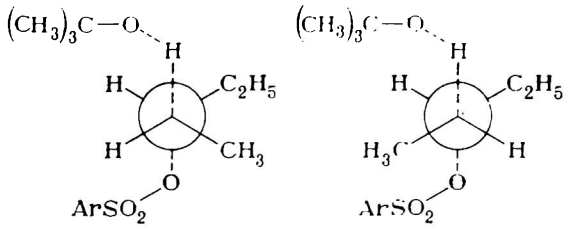

For compounds of the type $R—CH_2—CHX—R$, *two* conformations contributing to the *trans*-dehydrohalogenation can be built. Different (*cis-trans*-isomeric) olefins are formed from these conformations upon elimination of HX (see above).

The formation of the reaction conformations $\varphi^3$ and $\varphi^1$ is not equally probable in a general case since in the skew conformation the bulky substituents R are closer to one another than in the transoid conformation. From this it may be concluded that *trans*- and not *cis*-olefins are predominantly formed in such reactions, the shift in favour of the *trans*-isomer being the greater, the more bulky are the substituents R. The experimental material available in the literature supports this conclusion. For example:

| Compound | The ratio of *trans*- and *cis*-olefins |
|---|---|
| 2-Bromobutane ($R=CH_3$) | 6:1 |
| Phenylbenzylcarbinol ($R=C_6H_5$) | 100:1 |

Examples are however known, where reactions do not obey this regularity. Thus, Brown (28) observed the predominant formation of *cis*-olefins when aryl sulphonates were acted on by potassium *tert*-butoxide in *tert*-butanol. He explained this by the fact that of the two possible transition states in the elimination by the *E*2 mechanism (using 3-pentanol tosylate as an example) the more favourable is the state XI in

which the bulky *tert*-butyl and arylsulphonic groups may "turn aside" from the radicals $CH_3$ and $C_2H_5$ being in the skew position relative to them, whereas in the transition state XII the bulky substituents are blocked from both sides by the radicals:




XI XII

If ethoxide is used instead of *tert*-butoxide and ethanol instead of *tert*-butyl alcohol, this reaction, as usual, gives mainly *trans*-olefins.

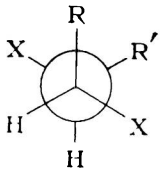
The starting compounds that participate in 1,2-eliminations are often compounds with two chiral centres and can therefore exist as two diastereomers: the *threo*-form (the racemate in symmetrical compounds) and the *erythro*-form (the *meso*-form in symmetrical compounds). Diastereomers behave differently in the course of elimination reactions. Thus, in the case of diastereomers of the general formula R—CHX—CHX—R, the dehydrohalogenation of the *erythro*-form (or the *meso*-form) occurs more slowly than the same reaction for the *threo*-form (racemic form):

| Formula | The ratio of the rates of elimination of HX from the *threo*- and *erythro*-forms |
|---|---|
| $C_6H_5-CO-CHBr-CHBr-CO-C_6H_5$ | 7:1 |
| $C_6H_5-CHBr-CHBr-CO-CH_3$ | 100:1 |
| $C_6H_5-CHCl-CHCl-C_6H_5$ | *meso*-Form (corresponding to the *erythro*-form) does not react |

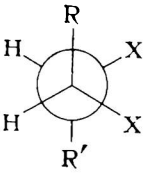
From the data given it is seen that the greater the effective size of the substituent ($C_6H_5 > C_6H_5CO$) the more prominent is the retardation of the reaction of the *erythro*-form as compared with the *threo*-form. This is because of the three possible conformations of the *threo*-form the more preferred one is the conformation XIIIb with the transoid arrangement of the leaving H and X, which is required for the elimination; the *erythro*-form exists mainly in the conformation XIVb

in which there are *no* conditions necessary for the transoid elimination of HX:

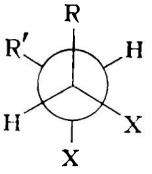
Conformations of *threo*-form




XIIIa

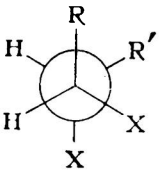



XIIIb

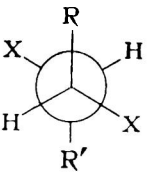



XIIIc

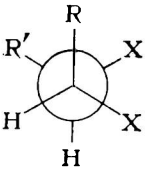
Conformations of *erythro*-form




XIVa




XIVb



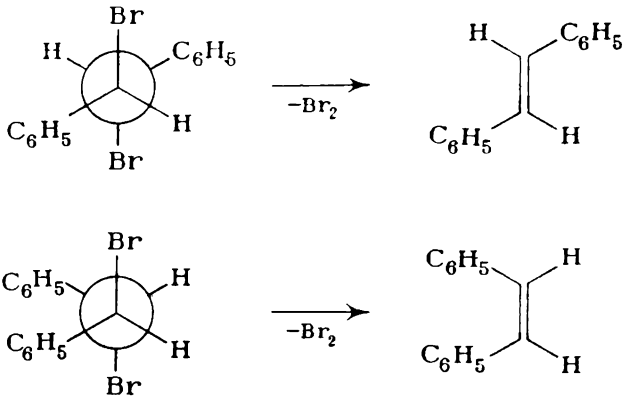

XIVc

It is necessary at this point to preclude the possible misunderstanding: one must not think that such a ratio of the reactivities of the *erythro*- and *threo*-forms is constant. This depends first on the concrete ratio of the effective sizes of the substituents and second on the reaction under consideration. Thus, if a different reaction is carried out on the diastereomers indicated above, say, dehalogenation, then the conformation of the *erythro*-form, XIVb, is found to have the transoid arrangement of the substituents favourable for such elimination, and it will in this case react *more readily* and more rapidly than the *threo*-form; the latter has first to pass from the most favourable conformation XIIIb to conformation XIIIa which turns out to be the less favourable the larger the effective volume of the substituents R and R′. It is for this reason that in the elimination of bromine from 1,2-dibromides under the action of potassium iodide in acetone the *meso*-isomers react faster than the racemic forms (29):

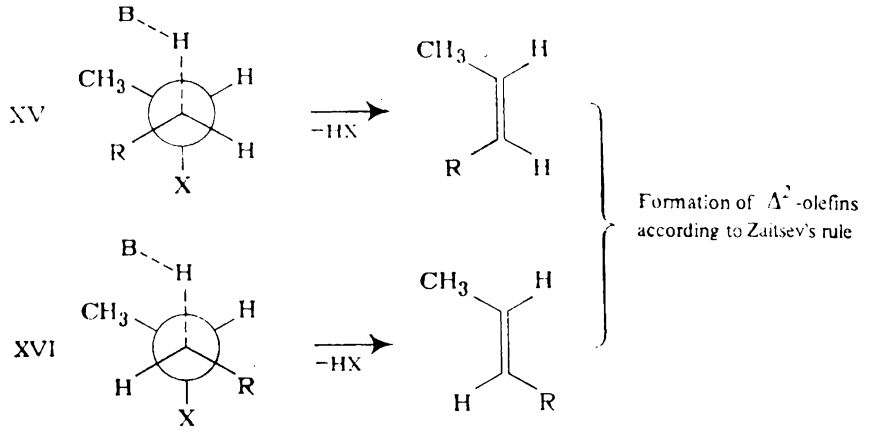
$$R{-}CHBr{-}CHBr{-}R \xrightarrow[-Br_2]{KI} R{-}CH{=}CH{-}R$$

| R | The ratio of the rates of elimination reactions of the racemate and *meso*-form |
|---|---|
| $CH_3$ | 1 : 2 |
| COOH | 1 : 4 |
| $C_6H_5$ | 1 : 100 |

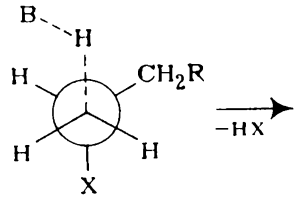
In this reaction, the *meso*-dibromide, according to its reaction conformation, gives a *trans*-olefin and the racemic dibromide gives mainly a *cis*-olefin:




As known, in elimination reactions one has to consider the possibility of two directions in the formation of a double bond, either in accordance with Zaitsev's rule (the elimination of hydrogen from the less hydrogenated carbon atom and the formation of the most alkylated ethylene) or in accordance with the Hofmann rule (the elimination of hydrogen from the most hydrogenated carbon atom and the formation of the least alkylated ethylene). Let us examine the transition states for an elimination reaction by the mechanism *E*2 for compounds R—$CH_2$—$CH(CH_3)$—X, which correspond to the directions of the reaction according to Zaitsev's rule and Hofmann's rule:



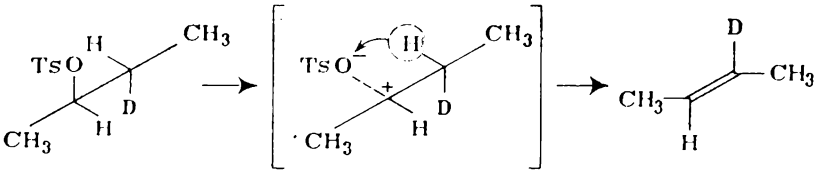
XVII




Formation of $\Delta^1$-olefins according to Hofmann's rule

$\Delta^2$-Olefins are more stable thermodynamically than $\Delta^1$-olefins. But in the transition states XV and XVI, which lead to the Zaitsev elimination, there are unfavourable skew interactions between R and X, whereas in the transition state XVII for the Hofmann elimination there are no such interactions. The steric hindrances for the approach of the proton-attracting base B are also different. Because of this, the steric factors play an important part in the selection of either of the two routes of elimination (although these factors are not the only ones). Thus, bulky bases attack the molecule predominantly from the periphery—in accordance with the Hofmann rule: therefore, when 2-bromobutane is acted on by alkoxides, the fraction of the 1-butene formed increases in passing from ethoxide to *tert*-butoxide. The increase in the size of the leaving group X contributes to the Hofmann elimination as well: in accordance with this, *butyl*-2-trimethylammonium (with bulky X) almost exclusively gives 1-butene, whereas from 2-halobutane (X is less bulky) there is formed 2-butene.

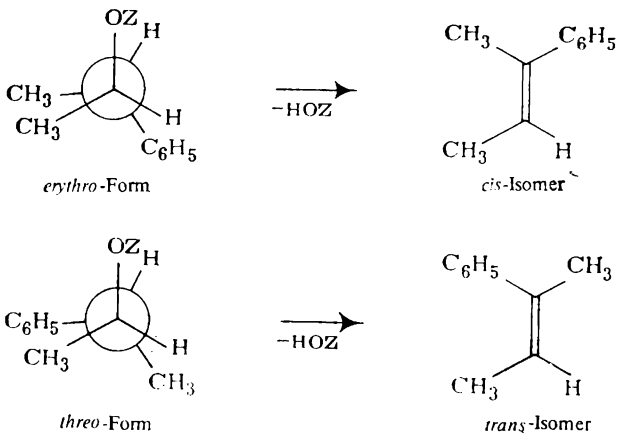
As has already been noted, *E*1 elimination reactions usually proceed non-stereospecifically. Let us consider, however, a case where the solvent has a low dielectric constant (which contributes to the stabilization of ion pairs) and a low basicity. In this case, only the anion X formed upon dissociation can play the role of the nucleophilic reagent for elimination of a β-proton, and it does actually remove the *nearest* β-proton, the one being in the cisoid (skew) position. Such a course of the reaction was observed for deuterium-labelled 2-butyl tosylates when the reaction was carried out in nitrobenzene:




The cisoid orientation of the groups to be eliminated in reactions by the *E*1 mechanism is especially characteristic of conversions in the

gas phase, a medium which has a minimum dielectric constant and is not basic at all.

The cisoid elimination is also typical of olefin-forming reactions occurring by way of thermal decomposition of xanthates (Chugaev reaction). This is shown, for example, by the study of olefin formation from xanthates of 3-phenyl-2-butanol. The reaction conformations for diastereomeric forms in the cisoid elimination must be as follows (Z corresponds to the group $C(=S)SR$):

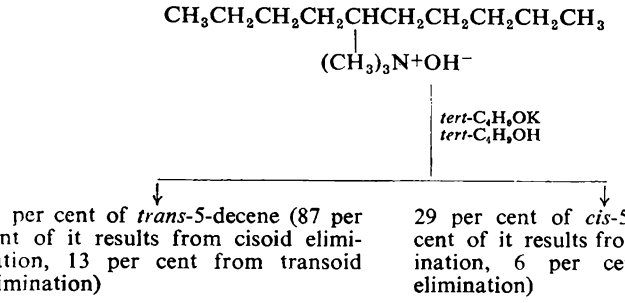



Not only are olefins of different configurations formed from the *erythro*- and *threo*-forms but the reaction rate for the *erythro*-form is greater since in the corresponding reaction conformation the phenyl group is eclipsed by hydrogen, which creates less steric hindrances than the eclipsing of the phenyl group by the methyl group present in the *threo*-form.

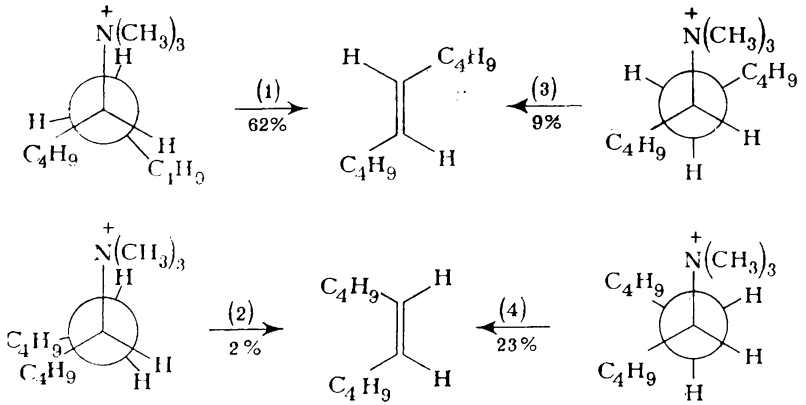
### 6.3.3. SYN-ANTI DICHOTOMY IN 1,2-ELIMINATION REACTIONS

In the 1960's there were published the works of Czechoslovak investigators, which cast doubt on the course of elimination reactions described in the previous section (see ref. 30 for a review article). Let us consider an example of the reaction between the base 5-trimethylammoniumdecane and potassium *tert*-butoxide in *tert*-butanol. This reaction yields a mixture of *cis-trans*-isomeric 4- and 5-decenes. The use of deu-

terium-labelled starting compounds (and other methods) has provided evidence to prove that the reaction is *not* a pure *trans*-elimination:


CH3CH2CH2CH2CHCH2CH2CH2CH2CH3
(CH3)3N+OH−
tert-C4H9OK
tert-C4H9OH
71 per cent of trans-5-decene (87 per cent of it results from cisoid elimination, 13 per cent from transoid elimination)
29 per cent of cis-5-decene (94 per cent of it results from transoid elimination, 6 per cent from cisoid elimination)

Using these data, one can calculate to what extent the four possible reaction conformations participated in the process of elimination (the extent of participation of the conformations is indicated under the corresponding arrows):




The principal direction of the reaction (pathway 1) is a cisoid elimination, the corresponding conformation being more favourable than the second possible eclipsed conformation leading to the other stereoisomer (pathway 2). About one-third of the molecules react by the scheme of transoid elimination in the skew conformation (pathway 4). The pathway 1 becomes more and more preferred with increasing strength of the base and with decreasing dielectric constant of the medium. The various leaving groups may be arranged in the following sequence: $Br < OTs < {}^{+}N(CH_3)_3$.

Based on their investigations, the Czechoslovak chemists have come to the conclusion that either the transoid or the cisoid elimination may prove to be preferred, depending on the structure of the substrate, the

nature of the leaving group, the reagent, and the solvent. Three cases are possible here:

(a) the transoid elimination, giving a mixture of *cis-trans* isomers;

(b) the cisoid elimination, giving a mixture of *cis-trans* isomers;

(c) the mixed cisoid-transoid elimination, in which both products are formed by the two pathways, but the *cis*-isomer is predominantly the product of the transoid elimination and the *trans*-isomer is mainly formed by way of cisoid elimination.

Case (a) corresponds to the *E*2-transoid elimination; it is well known and is often encountered, but it should not be regarded as absolutely general. It is important primarily with readily leaving groups (say, halogens, $OSO_2C_6H_4CH_3$) and solvents contributing to dissociation.

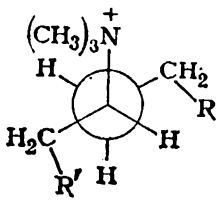
Case (b) describes intramolecular eliminations, as, for example, the formation of olefins from amine oxides (55).

Case (c), which was called "*syn-anti* elimination dichotomy" by the Czechoslovak authors, occurs predominantly with difficultly leaving groups (onium groups) when use is made of strong bases and solvents, which contribute little to dissociation.

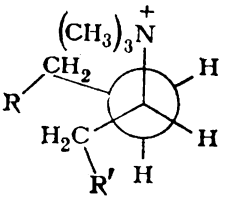
It has been noted lately that *syn-anti* dichotomy manifests itself with *any* leaving groups in solvents contributing to the formation of ion pairs (e.g., dimethyl sulphoxide) (31). Though some authors reject the role of ion pairs (32), a work has recently been published, in which there is given a direct experimental proof of the participation of ion pairs in *syn*-elimination processes; since this work is concerned with the formation of cyclic olefins, it will be discussed at a later time (see page 445).

With transoid elimination there prevails a reaction conformation with the skew arrangement of all the three substituents, R, R′, and $^+N(CH_3)_3$, which is therefore unfavourable because of spatial considerations. The participation of this conformation has been explained in several ways.

Bailey and Saunders (33) emphasized the fact that in the reaction conformation XVIII, which leads to the *trans*-isomer, the hydrogen to be eliminated is blocked from both sides (by the substituents R and R′), whereas in conformation XIX, which leads to the *cis*-isomer, the approach to this hydrogen is unhindered from one side:

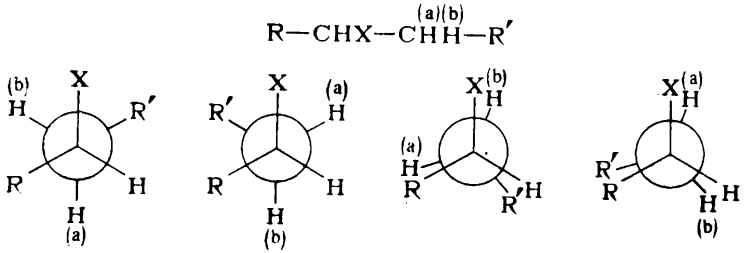



XVIII




XIX

Sicher maintains that a similar, but somewhat modified, model is possible: in conformation XVIII the repulsion between the groups $^{+}N(CH_3)_3$ and $CH_2R$ leads to the approach of $CH_2R'$ to the hydrogen to be eliminated and thus hampers the approach of the base required for the reaction to take place. In conformation XIX leading to the formation of the *cis*-olefin, the same interaction makes the removable hydrogen sterically more accessible. Sicher puts forward another explanation too, which is based on the possible differences between the reactivities of the two diastereotopic hydrogens of the $CH_2$ group taking part in the elimination. The reaction conformations for *trans*- and *cis*-eliminations will be written as follows:

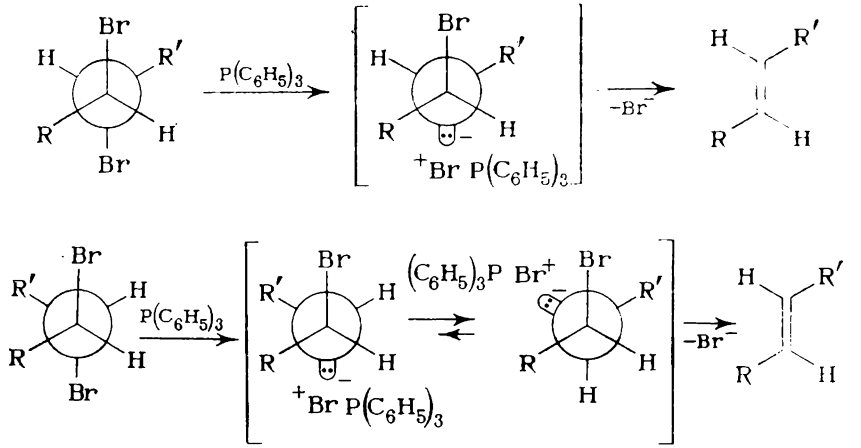



If the hydrogen $\overset{(b)}{H}$ is considered to be more reactive than the diastereotopic hydrogen $\overset{(a)}{H}$, it becomes understandable that *trans*-elimination must predominantly give a *cis*-olefin (the reaction conformation XXb) and *cis*-elimination, a *trans*-olefin from the reaction conformation XXIa. In principle, the differences in chemical properties between diastereotopic hydrogens are known (34). Wolfe (35) explains the specificity of elimination reactions from the standpoint of the **gauche effect** (see page 254).

A knowledge of the relationships for elimination reactions allows one, where necessary, to choose conditions favouring the preparation of the required isomer in the purest state possible. Thus, for example, cyclodecyl chloride when reacted with dicyclohexylamine in hexane (a strong base, a non-polar solvent) gives practically pure *trans*-cyclodecene (predominantly by way of *syn*-elimination). The reaction between the same chloride and potassium *tert*-butoxide in dimethyl sulphoxide (a polar solvent) yields mainly *cis*-cyclodecene (by way of *anti*-elimination) (36).

Interesting specific features have been revealed in studying the debromination of compounds of the type R—CHBr—CHBr—R′ by the action of triphenylphosphine (37). In this particular case, *both* diastereomers give the *trans*-olefin. The authors believe that the transiently

formed ion pair is sufficiently stable to adopt the more favourable transoid conformation prior to the elimination of the second bromine atom:




The mechanism and stereochemistry of *E*2 elimination reactions are substantially influenced by the nature of the transition state (the extent of the double-bond character in it). We shall not consider this problem in more detail; the reader is referred to one of the works, which offers some details of the approach to this problem (38).

## 6.4. STEREOCHEMISTRY OF ADDITIONS TO DOUBLE BONDS

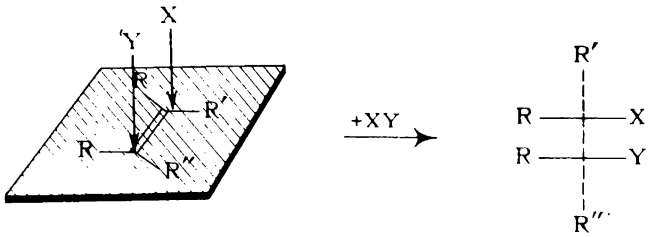
### 6.4.1. GENERAL

When dealing with reactions of addition to the double bond, we are faced with the problem that has been discussed in the section devoted to additions to the triple bond: whether both entering particles approach the double bond from the same side (*cis*-addition) or from opposite sides (*trans*-addition). This problem has been studied since the end of last century; it has been established that, depending on the type of the reagents being added and on the structure of olefins, both types of addition may be observed.

The steric course of the addition across the double bond can be established *only* in those cases where the compound resulting from the addition reaction has two asymmetric atoms, i.e., when *threo*- and *erythro*-isomers may be formed (or racemic and *meso* forms in the case of symmetrical structures). The formation of this or that form depends

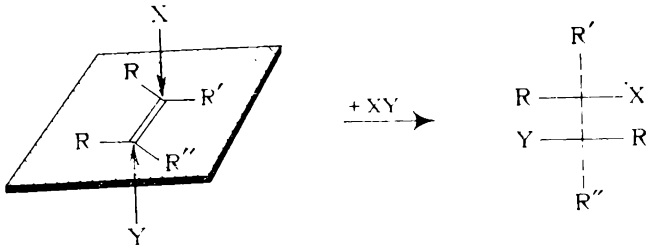
on the configuration of the olefin and the mechanism of the reaction. In a general case, the following variants may be encountered.

1. *cis*-Addition to a *cis*-olefin with the formation of an *erythro*-isomer:



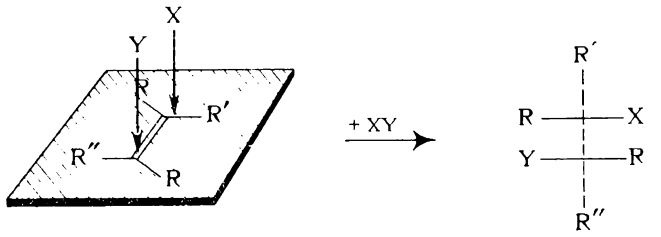

A special case here is the formation of a *meso*-form if $R' = R''$ and $X = Y$.

2. *trans*-Addition to a *cis*-olefin, which leads to the formation of a *threo*-isomer:

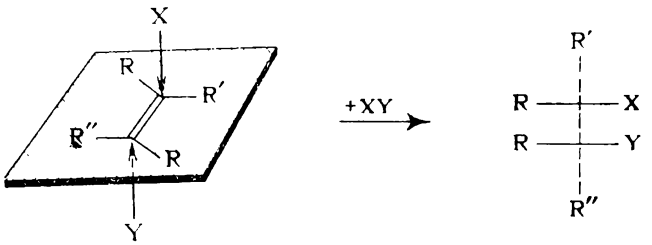



A special case here is the formation of a racemate if $R' = R''$ and $X = Y$.

3. *cis*-Addition to a *trans*-olefin with the formation of a *threo*-form (of a racemate in a special case):

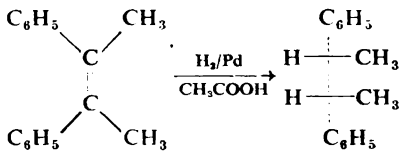


4. *trans*-Addition to a *trans*-olefin with the formation of an *erythro*-isomer (of a *meso*-form in a special case):

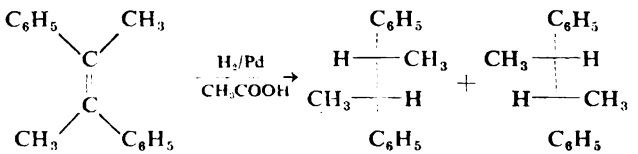



6.4.2. CIS-ADDITION REACTIONS

The **hydrogenation** over a catalyst usually proceeds as a *cis*-addition; for example:



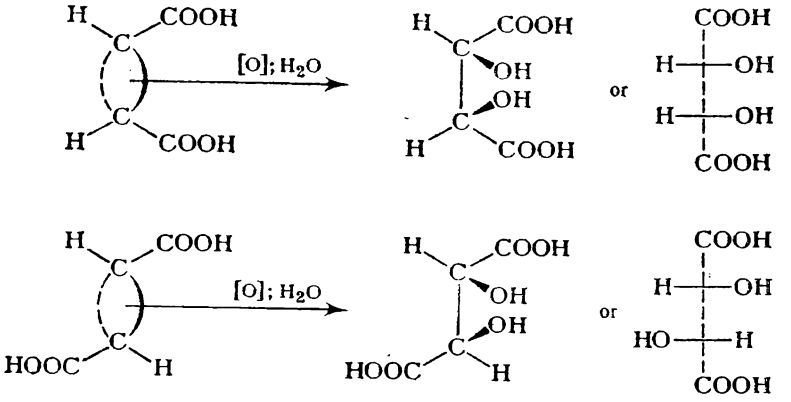

*meso*-2,3-Diphenylbutane




Racemic 2,3-Diphenylbutane

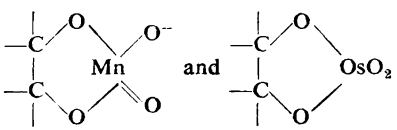
The rule concerning the *cis*-addition of hydrogen upon catalytic hydrogenation operates in the majority of cases, but there are exceptions which will be discussed in the section devoted to cycloolefins.

The **hydroxylation** of olefins (by the action of potassium permanganate or osmium tetroxide) also proceeds in *cis*-fashion. The oxidation of maleic acid by permanganate affords *meso*-tartaric acid, whereas similar oxidation of fumaric acid yields racemic tartaric acid:

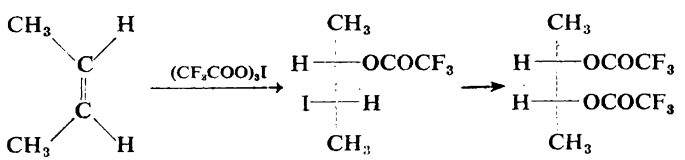



Apart from D-tartaric acid shown in the above scheme, the oxidation of fumaric acid may also give (with equal probability) L-tartaric acid (the approach of both hydroxyl groups from behind the plane of the drawing), and therefore the reaction results in the formation of a racemate. It is this reaction with which Wislicenus began (in 1887) studying the stereochemistry of the addition to the double bond. Wislicenus thought the result obtained to be natural and the only one conceivable. That two particles of the same reagent can approach the double bond from opposite sides was considered to be impossible at those times. Thus, in 1888 Auwers and Meyer called the concept of *cis*-addition "a fruitful idea" and considered this type of addition to be the only one possible.

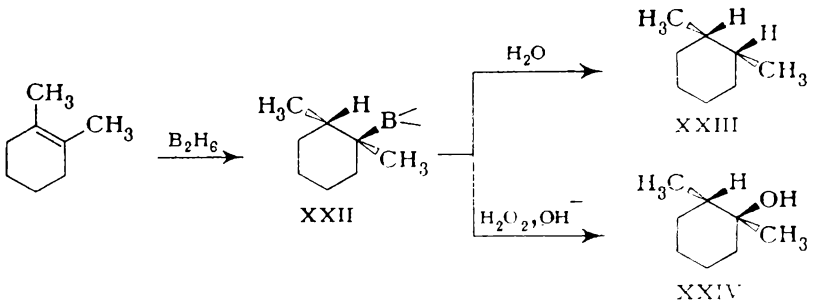
Today we know that *cis*-hydroxylation occurs because intermediate products of cyclic structure are first formed:




*cis*-Addition was also observed when alkenes were reacted with compounds of trivalent iodine, say, iodo-tris-trifluoroacetate (39). It is believed that there first takes place the *trans*-addition of the reagent across the double bond, this being followed by the $S_N2$ replacement of iodine by the trifluoroacetoxy group with inversion of configuration:



The hydroboration reaction discovered in the sixties also proceeds according to the scheme of *cis*-addition:




The hydroboration reaction consists in the *cis*-addition of the hydrogen atom and the boron-containing residue to the double bond. The reaction product XXII when decomposed by water exchanges the boron-containing group for hydrogen and is converted into a saturated hydrocarbon XXIII, and on oxidation with hydrogen peroxide in alkaline medium the boron-containing group is replaced by a hydroxyl group and the alcohol XXIV is formed.

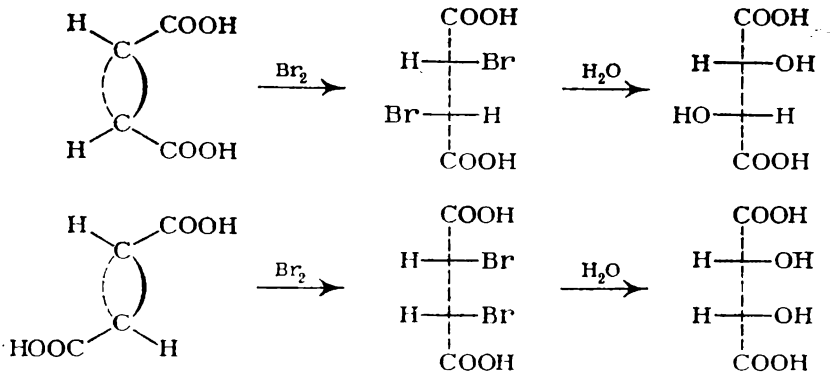
In practice, the hydroboration is conducted with the aid of various boron hydrides rather than with free boranes (these are difficult to prepare and inconvenient to handle). Besides, intermediate organoboron compounds XXII are, as a rule, trialkylboron compounds of the type $R_3B$; the monosubstituted product in the above scheme is given only for more clarity. Compounds of the type $R_2BH$ with an optically active radical (R = α-pinene residue) were found to be exceptionally active agents for carrying out asymmetric synthesis (see Chapter 2).

The *cis*-addition is also characteristic of the reaction of carbenes with olefins (40).

### 6.4.3. TRANS-ADDITION REACTIONS

The addition of the diverse reagents much more often proceeds according to the *trans*-scheme. This refers, for example, to electrophilic addition (for a review, see ref. 41) of halogens, halogen acids, water, hypohalides, phenylsulphenyl chlorides, $C_6H_5SCl$. The simplest example is the action of bromine on maleic and fumaric acids, which results

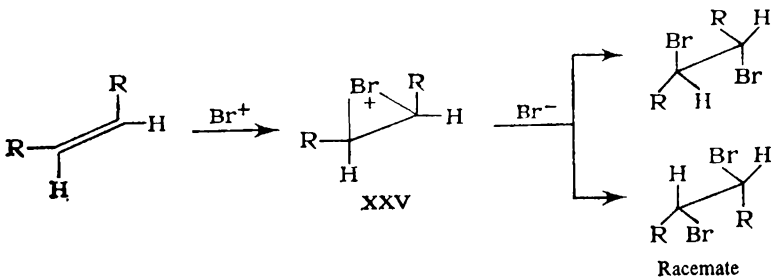
in the formation of racemic and *meso* products, respectively:



With the purpose of configuration determination, dibromosuccinic acids were subjected to hydrolysis. This involves the breaking of the bonds of the asymmetric atom and therefore a Walden inversion is possible. This however does not interfere with the conclusion that under the action of bromine there must be observed *trans*-addition since upon hydrolysis either Walden inversion must occur at both asymmetric centres or no Walden inversion must take place at all at both centres. Therefore, independently of whether Walden inversion takes place or not, *meso*-tartaric acid can be obtained only from mesodibromosuccinic acid and racemic tartaric acid only from racemic dibromosuccinic acid.

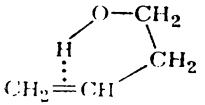
Bromine acts in a similar manner on *cis*- and *trans*-2-butenes.

The scheme of *trans*-addition is also followed by the reaction of the ethyl ester of *trans*-cinnamic acid with bromosuccinimide; this reaction gives 80 per cent of the *erythro*-isomer (42). It is believed that the addition proceeds via the bromonium ion XXV which is approached by the bromide ion from the rear side at the final stage of the reaction:

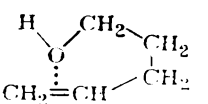


The *trans*-addition of halogen azides $X—N_3$ to olefins also proceeds through intermediates of the type of halogenonium ions (43). The addition of halogen acids is also *trans*. An example is the reaction of deuterochloride with diethyl esters of fumaric and maleic acids (44). The reduction of the same esters by the action of $(C_4H_9)_3SnH$ in deuterated methanol has been found to be a non-stereospecific reaction (45).

In some compounds of the type $CH_2=CH—(CH_2)_n—X$ there is observed a substantial effect of the functional group X on the reactivity of the double bond. Since ordinary electronic effects cannot account for this influence, the concept of the existence of conformations in which the functional group interacts with the double bond has been put forward (46):



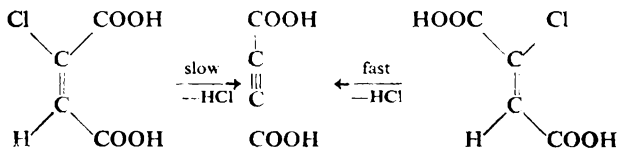
Fall of electron density of double bond



Rise of electron density of double bond

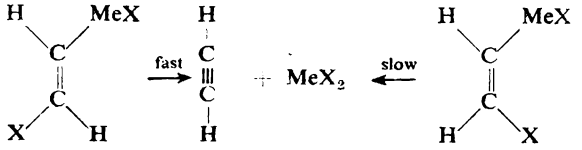
## 6.5. STERIC DIRECTION OF ELIMINATION REACTIONS OF OLEFINS

We have already said that originally the addition to the double bond was thought to be exclusively *cis*. Elimination reactions were treated in just the same manner. On the basis of the seemingly "natural" and "obvious" considerations, it was thought that the elimination proceeded most readily if the atoms or groups to be eliminated are close together. In actual fact, as was shown by Michael (1895), the *trans*-elimination occurs with great ease. Therefore, for example, the elimination of hydrogen chloride from chlorofumaric acid is about 50 times as fast as that from chloromaleic acid:




Numerous examples that confirm the preference of *trans*-elimination from olefins have been collected in the works of Pfeiffer and Frankland. At a later time, A. N. Nesmeyanov and coworkers (47) found that the

elimination of salts from the *trans*-forms of chlorovinyl organometallic compounds proceeds more readily than from the *cis*-forms:

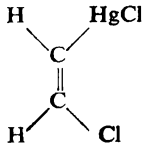



## 6.6. STERIC DIRECTION OF SUBSTITUTION REACTIONS AT THE OLEFINIC CARBON ATOM

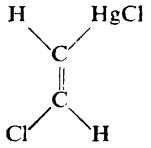
Compounds of the ethylene series are known to be characterized mainly by addition reactions, the steric directedness of which was discussed in Sec. 6.4. Substitution reactions are also known to take place. In those cases where the atom or group to be replaced stands directly at a double bond, there arises a problem similar to the problem of Walden inversion in reactions affecting the chiral centre: Is the configuration of the starting compound retained in the reaction product or not?

The difficulty of the investigation of substitution processes taking place at the olefinic carbon atom is primarily that most of the reactions, the formal result of which boils down to the substitution at the olefinic carbon atom, in fact proceed via the addition stage followed by elimination. This course is taken, for example, by the sulphonation carried out with the aid of complexed sulphur trioxide, the acylation under the conditions of the Friedel-Crafts reaction, the azo coupling with diazo compounds. For a large number of other reactions, it has not been established whether they take place by way of direct substitution or not; this refers to the nitration of olefins, the halogenation with the aid of bromosuccinimide, the Meerwein reaction (the interaction with diazo compounds). The most suitable for the study of the steric directedness of substitution reactions at the olefinic carbon atom are reactions involving the exchange of metals in organometallic compounds of the type X—CH=CH—MeX.

The starting compounds in the works of A. N. Nesmeyanov and his coworkers were geometrically isomeric β-chlorovinylmercurichlorides, for which the following configuration has been conclusively proved:



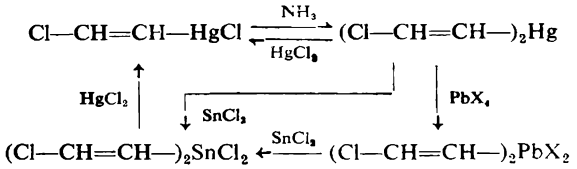

*cis*-Form
(m.p. 79°C; dipole moment 2.76 D)




*trans*-Form
(m.p. 124°C; dipole moment 1.64 D)

The study of the stereochemistry of the reactions of these and similar compounds has enabled the following rule to be formulated, which determines the steric features of substitution reactions occurring at the olefinic carbon atom (the **Nesmeyanov-Borisov rule**): electrophilic and radical substitution reactions at the olefinic carbon atom proceed with retention of configuration.

The most spectacular proof of the validity of this rule is the result obtained by studying the isotopic exchange of mercury for radioactive mercury in geometric isomers of β-chlorovinylmercurichloride. In this reaction, the *trans*-isomer gives only the *trans*-isomer labelled with radioactive mercury, and the *cis*-isomer affords only the labelled *cis*-isomer (48). Another proof is provided by the reactions of exchange of metals carried out with chlorovinylmercurichlorides, which result in the reversion to the starting compound through different numbers of stages; for example,

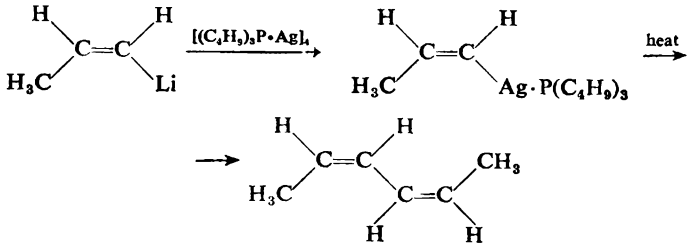



After the completion of any series of reactions involving any number of intermediates, a chlorovinylmercurichloride having the configuration of the starting compound is invariably recovered. It is difficult to assume that in the course of conversions via various numbers of intermediate stages the interconversion of the *cis-trans* configurations always took place an even number of times, which in principle could have provided the reversion to the original geometric configuration. On the contrary, the conclusion that the configuration is retained in any one of these conversions is natural.

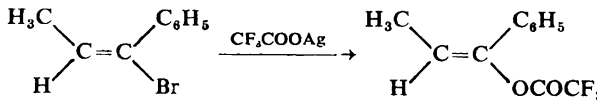
It is important to carry out investigations with *both* geometric isomers since the retention of the configuration of one of them is not yet a final conclusive proof of the inevitability of the same steric course of the reaction with the other isomer: *both* isomers may be found to react with the formation of the same product which is thermodynamically more stable. In such a case, one of the geometric isomers will react with retention and the other with inversion of configuration.

Having returned to this problem at the end of the sixties, A. N. Nesmeyanov once again confirmed the validity of the rule with strict control of the stereochemical purity by the NMR method (49). The validity of the Nesmeyanov-Borisov rule has been verified by other authors for other types of reactions as well. For instance, it has been established (50) that the configuration at the olefinic carbon atom is retained when

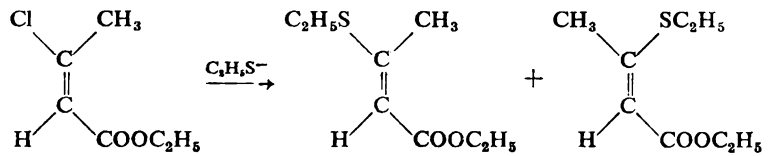
lithium in lithiumolefins is exchanged for silver, this being followed by the formation of a carbon-carbon bond:



The Nesmeyanov-Borisov rule is also applicable to the reaction of nucleophilic replacement of bromine by the trifluoroacetoxy group (51):



The other isomer also reacts with retention of configuration. The reaction is conducted at a low temperature (—78°C); the authors maintain that this reaction proceeds by the $S_Ni$ mechanism with the intermediate formation of the allyl cation. Another example of retention of configuration in a nucleophilic substitution reaction is the action of ethyl mercaptan on the ester of β-chlorocrotonic acid (52):



*cis*-Ester — XXVI 85% — XXVII 15%

The analogous reaction of the *trans*-form of the ester yields 92 per cent of the isomer XXVII and 8 per cent of the isomer XXVI, i.e., the configuration is also retained. With oxygen-containing nucleophiles ($C_2H_5O^-$, $C_6H_5O^-$), however, the same equilibrium mixture is formed from both isomers in the same reaction, i.e., the reaction is no longer stereospecific.

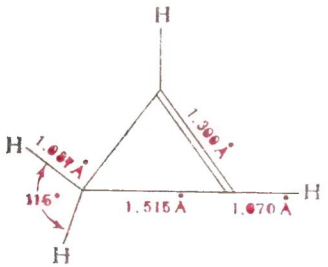
The loss of stereospecificity is in many cases associated with the fact that the reaction proceeds by way of initial elimination of HX, and the

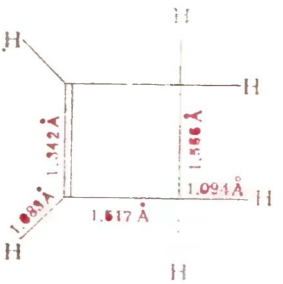
stereochemical result then becomes dependent on the stereochemistry of the addition to the triple bond (see page 415). Other reactions occur through the addition of the reagent across the C=C bond with subsequent elimination — the stereospecificity is then determined by the stereochemistry of addition and elimination reactions described earlier (see pages 418 and 430). Additional data on the stereochemistry of addition reactions are given by Ingold (25).

## 6.7. STEREOCHEMISTRY OF COMPOUNDS WITH A DOUBLE BOND IN THE RING

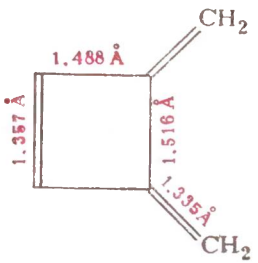
### 6.7.1. RING CONFORMATIONS

The simplest unsaturated rings, cyclopropene and cyclobutene, have the following geometric parameters (85):



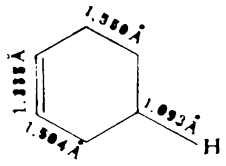



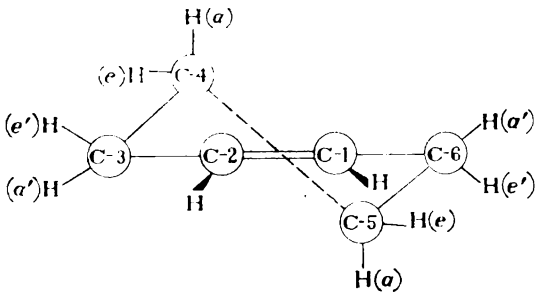

Like cyclopropane, its unsaturated analogue is also built through the participation of banana bonds (bent bonds) (54). Just as in the case of its saturated analogue, in cyclobutene we again encounter a certain extension of the C—C bond. According to electron diffraction data, unusual bond lengths have also been detected in 3,4-dimethylidenecyclobutene, $C_6H_6$ (the isomer of benzene!) (55):



The most favourable conformation for cyclopentene is considered to be the envelope conformation (56) which is also characteristic of the saturated analogue. When a carbonyl group appears in the cyclopentene ring, the ring becomes planar (57).

One of the thoroughly studied compounds with a double bond in the ring is cyclohexene. It has been found, by means of X-ray and electron diffraction methods, that cyclohexene has the half-chair conformation [(*a*) and (*e*) denote, as before, the axial and equatorial positions of the hydrogen atom; (*a'*) and (*e'*) specify, accordingly, the pseudoaxial and pseudoequatorial positions]. The geometrical parameters of the cyclohexene molecule are given in the usual "planar" formula of the compound:

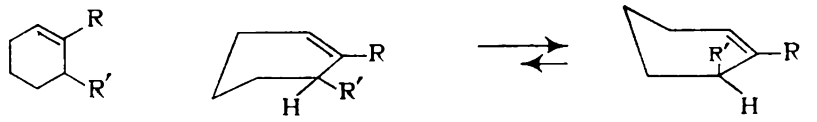



The methylene groups C-3 and C-6, which are in the allylic position relative to the double bond, have their hydrogens in the so-called pseudoequatorial and pseudoaxial orientation. The only true equatorial and axial positions in cyclohexene are those at atoms C-4 and C-5. Jensen and Bushweller (59) determined the parameters of the thermodynamical equatorial-axial equilibrium for 4-halogenocyclohexenes. The values obtained for the conformational energies are close to those found for the corresponding derivatives of cyclohexane (in kJ/mole): 1.16 for 4-fluorocyclohexene; 2.22 for 4-chlorocyclohexene; 2.00 for 4-bromocyclohexene; 1.96 for 4-iodocyclohexene. Based on IR and Raman spectral data, Pentin (60), however, found a substantially lower conformational energy for 4-chlorocyclohexene (about 0.8 kJ/mole).

In estimating the preferred conformations of substituted cyclohexenes, use is made of the concept of **allylic strain** (for a review article, see ref. 61). Structures of the type XXVIII exhibit $A^{1,2}$-strain; what is meant here is the unfavourableness of the equatorial orientation of the sub-

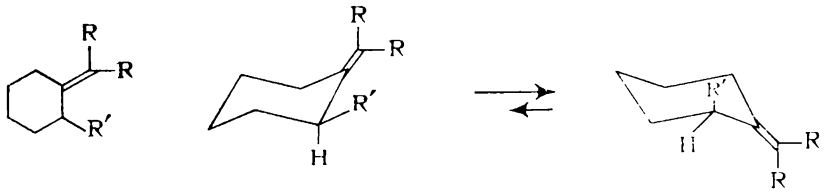
stituent R′ in the allylic position because of its closeness to the vinyl substituent **R**:



XXVIII XXVIIIa XXVIIIb

As a result, with bulky R and R′ the more favourable conformation is conformation XXVIIIb in spite of the axial orientation of the substituent **R′**.

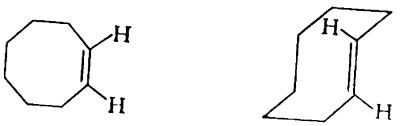
Structures of the type XXIX exhibit $A^{1,3}$-strain. This strain is responsible for the fact that with large R and R′ the conformation XXIXb with the axial orientation of the substituent R′ is the more preferred one:



XXIX XXIXa XXIXb

Introduction of *two* double bonds into a six-membered ring makes it even more planar. Thus, 1,4-cyclohexadiene has been found to be practically flat (62). And the double bonds adjacent to the ring do not change its conformation significantly. For example, cyclohexane-1,4-dione has the usual chair conformation (63).

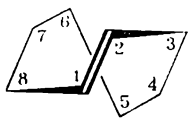
According to NMR spectral data, the chair conformation is assigned to **cycloheptene** (64), the boat conformation to cycloheptatriene (65). **Cyclooctene** is known to have two geometric isomers:



*cis-* *trans-*

*trans*-Cyclooctene, unlike ordinary olefins, has a considerable dipole moment (0.8 D).

*trans*-Cyclooctene is capable of existing as a pair of optical antipodes. But what is the nature of asymmetry of this compound? In simple olefins, the plane containing unsaturated atoms and their four nearest substituents is the plane of symmetry of the molecule: olefins, even those of the type ABC=CDE, are not optically active. The situation is different if the double bond is part of not too large a ring: the polymethylene bridge joining the ends of the double bond swings out of the plane and the entire molecule becomes asymmetric. Optically active *trans*-cyclooctene is just an example of compounds of this type (66). For this compound to be prepared, use was made of a complex of racemic *trans*-cyclooctene with $PtCl_2$ and (—)-α-phenylethylamine; in another method, the starting material was optically active *trans*-cyclooctane-1,2-diol (67). The absolute configuration and conformation of (—)-cyclooctene have been elucidated by means of the X-ray diffraction technique; they are expressed by the following formula (68):




The results of circular dichroism measurements (69) have also been used to calculate the absolute configuration of *trans*-cyclooctene (70); the result obtained coincides with that afforded by the X-ray diffraction method. The configuration deduced from ORD data in an earlier work (71) was incorrect (for the conformations of *trans*-cyclooctene and its homologues with a large number of members in the ring, see ref. 72).

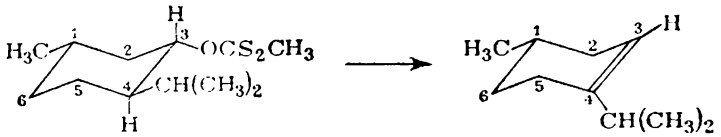
In passing to such homologues the mobility of the ring increases and stable, optically active compounds can no longer be obtained. *trans*-Cyclononene exists in an optically active form only at —80°C, the half-period of its racemization at 0°C being 4 min (for *trans*-cyclooctene it equals $10^5$ years!). The half-period of racemization of *trans*-cyclodecene is 20 sec and it cannot be prepared at all in an optically active form (73).

When a substituent is introduced into *trans*-cycloalkenes, conditions are created for the existence of diastereomeric forms: such forms are stable in the case of *trans*-cyclooctene; for *trans*-cyclodecene, the equilibrium of the diastereomers has been revealed only with the aid of NMR spectroscopy (74).

### 6.7.2. STEREOCHEMISTRY OF FORMATION OF CYCLOOLEFINS

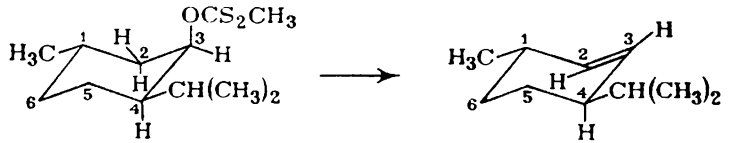
1,2-Elimination reactions that lead to the formation of cycloolefins exhibit, in general, the same stereochemical features as in the case of

reactions leading to acyclic olefins (see Sec. 6.3.2). These regularities, however, are more prominent in cyclic compounds because of their lower conformational mobility. It is compounds of the cyclohexane series that were used by Hückel (75) as early as 1940 in his pioneering study of the stereochemistry of 1,2-eliminations. He found that the pyrolysis of menthyl xanthate proceeds in accordance with Zaitsev's rule: in this case the hydrogen atom at C-4 is in the skew position to the xanthate group and can participate in the cisoid elimination characteristic for the given reaction:



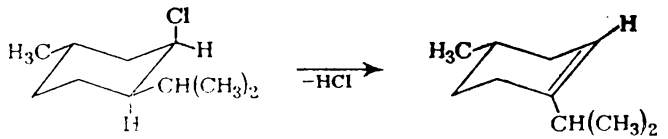

Menthyl xanthate — 3-Menthene

Neomenthyl xanthate has *no* hydrogen atom at C-4 arranged in the manner required for the cisoid elimination and therefore one of the hydrogens at C-2 takes part in the reaction:




Neomenthyl xanthate — 2-Menthene

Hückel observed the transoid elimination in reactions of elimination of hydrogen chloride from menthyl chloride and neomenthyl chloride. This part of his work was later developed by Hughes and Ingold (25). Neomenthyl chloride gives 3-menthene as the result of the *E*2-*trans*-elimination in accordance with Zaitsev's rule:

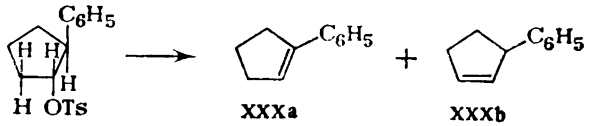



Neomenthyl chloride — 3-Menthene

In menthyl chloride, the hydrogen atom at C-4 cannot participate in the transoid elimination, and therefore the hydrogen atom at C-2 is involved in the reaction and 2-menthene is formed.

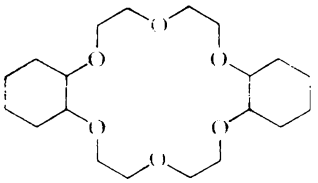
Under the conditions of the *E*1 elimination the reaction becomes non-stereospecific: from the base of trimethylmenthylamine there is formed a mixture of 32 per cent of 2-menthene and 68 per cent of 3-menthene.

In studying the elimination reactions for *trans*-2-phenylcyclopentyl tosylate (76), interesting observations were made, which threw light on the role of ion pairs in 1,2-elimination reactions:




XXXa XXXb

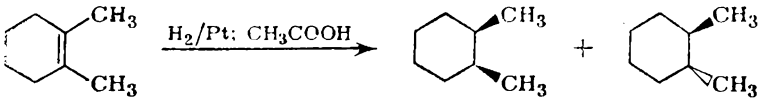
The action of potassium *tert*-butoxide in *tert*-butanol gave 90 per cent of the cisoid elimination product XXXa and 10 per cent of the transoid elimination product XXXb, whereas the same treatment in the presence of the "crown" ether



gave 30 per cent of XXXa and 70 per cent of XXXb. "Crown" ethers exhibit the unique property of binding cations in their inner cavity, thereby breaking down the ion pairs. The fact that the presence of "crown" ethers diminishes the fraction of the cisoid elimination product points to the important role of ion pairs in this process, just as was assumed by Závada.

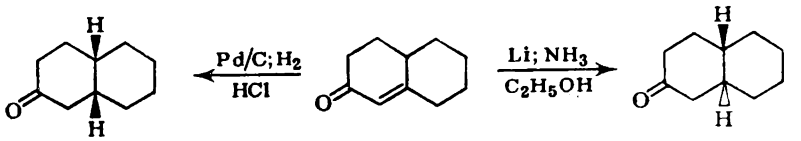
### 6.7.3. REACTIONS OF CYCLOOLEFINS

The stereochemical features of reactions of cycloalkenes differ noticeably from the steric direction of the corresponding reactions of non-cyclic compounds with a double bond. Thus, in contrast to olefins (see page 432), the catalytic hydrogenation of cycloalkenes gives appreciable amounts of *trans*-addition products; for example,

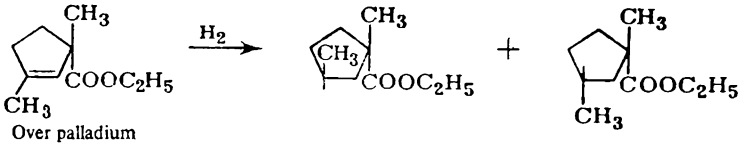



82-95% 5-18%

By reducing the double bond in $\Delta^{1(9)}$-2-octalone it is possible to prepare either *trans*-2-decalone or its *cis*-isomer, depending on the reagent used:

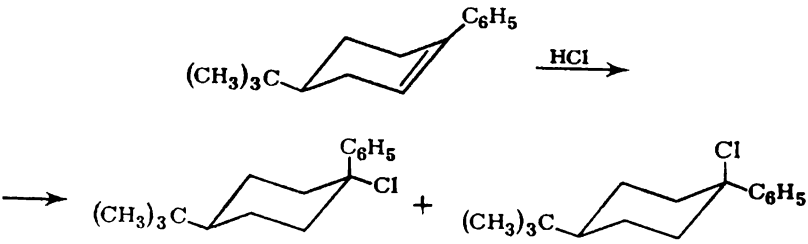



In the catalytic hydrogenation of 1-carbethoxy-1,3-dimethyl-2-cyclopentene, the ratio of the stereoisomers formed depends on the nature of the catalyst used (77):



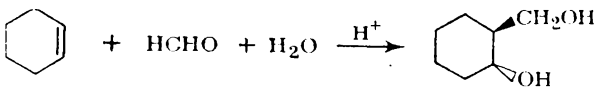

Over palladium charcoal in $CH_3COOH$ . . . . . 43 % 57 %
Over platinum in $CH_3COOH$ . . . . 27 % 73 %

The action of hydrogen chloride on 1-phenyl-4-*tert*-butylcyclohexene gave two stereoisomers: *cis*- and *trans*-1-chloro-1-phenyl-4-*tert*-butylcyclohexanes (78):

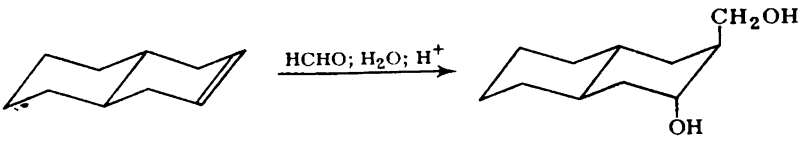



The electrophilic addition of chlorine, bromine, and hypochlorous and hypobromous acids to cycloalkenes occurs by the *trans*-scheme. It has been studied mainly on polycyclic steroid compounds.

The Prins reaction also takes place by the *trans*-scheme; for example,

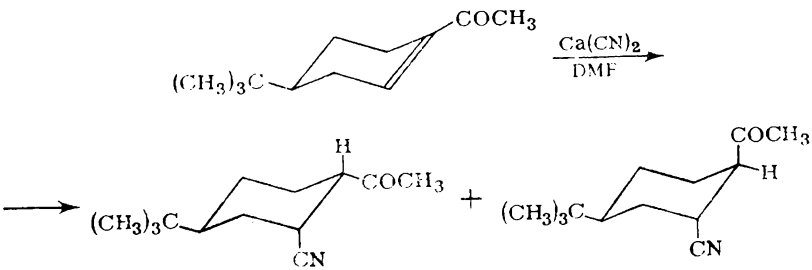


It is interesting that the Prins reaction in the rigid system of $\Delta^2$-*trans*-octalene, which also proceeds by the *trans*-addition scheme, yields a diaxial (thermodynamically less favourable) product (79):

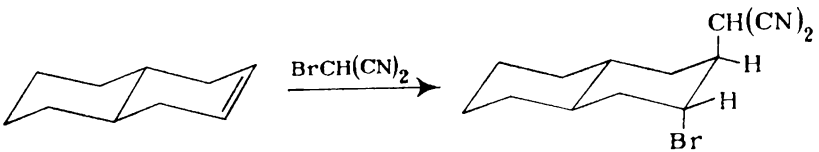



This clearly indicates that here steric rather than thermodynamic control occurs. The *trans*-scheme is also followed by the addition of peracids, and acyl chlorides under the conditions of the Friedel-Crafts reaction (80).

A characteristic feature of most reactions of addition to compounds of the cyclohexene series is the **axial approach** of the reagent. Apart from the examples given above, this may also be illustrated by the reaction of nucleophilic addition of hydrogen cyanide (81):

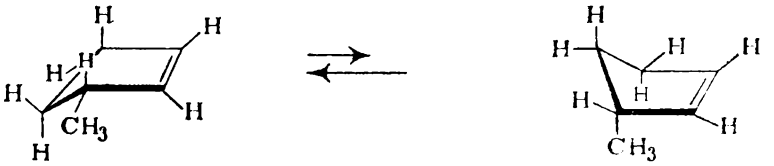



The radical addition of the dinitrile of bromomalonic acid, $BrCH(CN)_2$, to cyclohexene was found to be non-stereospecific — the *cis*- and *trans*-isomers of 2-bromo-1-dicyanomethylcyclohexane are formed in nearly equal quantities. But in the case of $\Delta^2$-*trans*-octalyne, the process is completely stereospecific: the *trans*-addition yields exclusively the diaxial product (82):

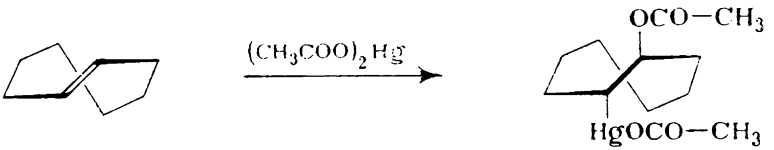



The epoxidation of 3-methylcyclopentene yields predominantly an isomer with the *cis*-arrangement of the methyl and epoxy groups, which

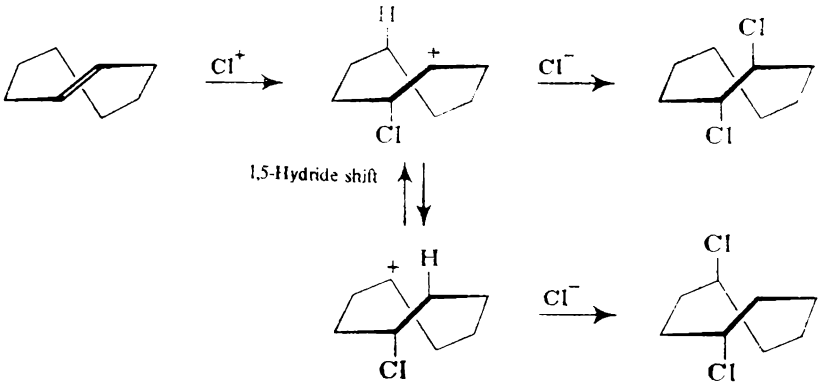
must have been less favourable (83). This result has been interpreted from the standpoint of the prevalence of the conformation shown on the left (which is more favourable because of the pseudoequatorial orientation of the methyl group) and the approach of the reagent to it predominantly from below since the approach from above is hindered by the pseudoaxial hydrogen atoms:



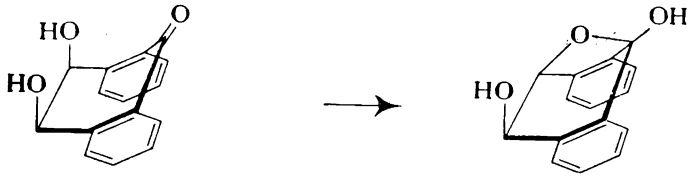
Interesting data have been obtained in a study of the hydroxymercuration of optically active *trans*-cyclooctene (84). This reaction proceeds by the scheme of transoid addition, the optical purity of the reaction product being dependent on the solvent: it is 98 per cent in methanol and 5 per cent in methylene chloride:




Transannular effects manifest themselves in the properties and reactions of *trans*-cyclooctene: they are noticeable, for example, in the NMR spectra (85), in the addition of chlorine (86), in the course of which up to 10 per cent of 1,4-dichlorocyclooctane is formed:



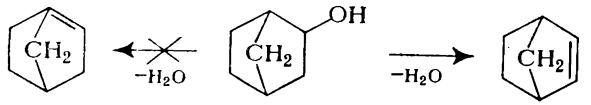
The signs of transannular interaction have been observed in a seven-membered ring in the case of formation of cyclic semi-ketals (87):




6.7.4. BREDT'S RULE

Of importance in bridged systems with a double bond is the *Bredt rule* which states that bridged systems having a double bond at the bridgehead position cannot exist (88).

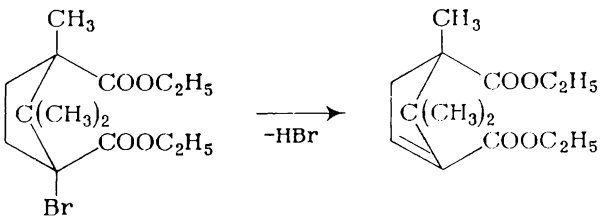
To illustrate, we shall begin with a simple example. Let us assume that we wish to carry out the dehydration of norborneol with the formation of a double bond. One would think that in accordance with the usual direction of such reactions the elimination of hydrogen should have occurred from the CH group (in accordance with Zaitsev's rule). In actual fact the elimination takes place from the $CH_2$ group:



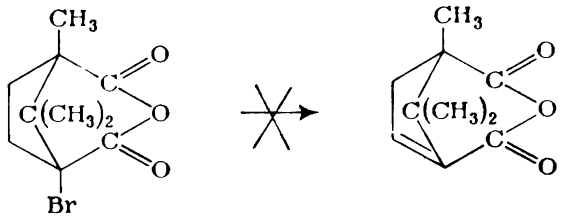

XXXI

The impossibility of formation of structure XXXI is just a demonstration of the Bredt rule.

Such deviations in the occurrence of simple reactions, which are accompanied by the formation of double bonds, became known as early as the beginning of this century. Thus, in 1902 Bredt noted the difference in the behaviour of the esters of bromocamphoric acid and its anhydride. Whereas, for example, the action of alkaline agents on the diethyl ester of bromocamphoric acid, XXXII, results in the elimination of hydrogen bromide from it, the action of the same reagent on the anhydride of bromocamphoric acid, XXXIII, fails to eliminate hydrogen bromide:

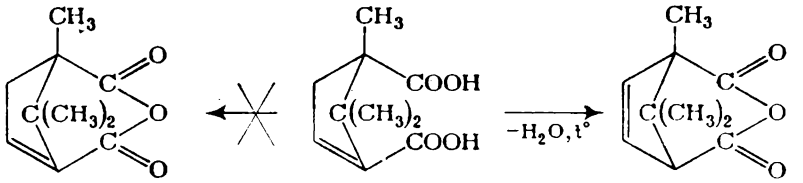



XXXII



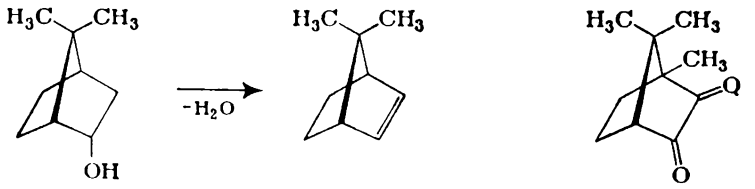
XXXIII

Later, Bredt observed that unsaturated acid XXXIV was incapable of cyclization to an anhydride under ordinary conditions. Under forcing conditions (distillation at atmospheric pressure) the anhydride forms with concomitant migration of the double bond to a non-bridgehead position and the reaction leads to compound XXXV:



XXXIV XXXV

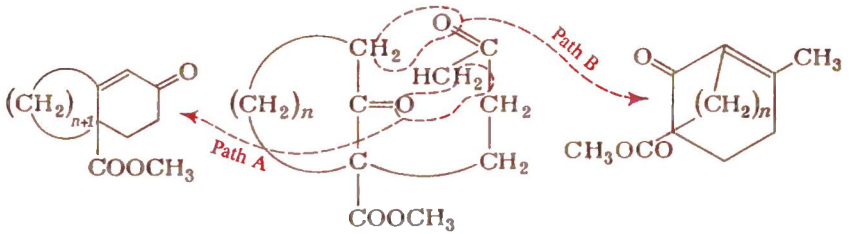
The Bredt rule has played an important part in the elucidation of the correct formulas of many derivatives of the terpene series. Thus, it has long been known that the loss of the elements of water in terpene alcohol camphenilol XXXVI gives rise to the unsaturated hydrocarbon "camphenilene", $C_9H_{14}$, which was assigned different structures in a number of works. Meerwein (1914) analysed the structures proposed in the light of Bredt's observations (we mean here the observations made by Bredt and not the rule which had not been clearly formulated at the time) and rejected them. Meerwein made a suggestion, which was subsequently confirmed, that "camphenilene" is in fact the long-known hydrocarbon santene XXXVII.



XXXVI XXXVII XXXVIII

That camphorquinone XXXVIII cannot be brominated under ordinary conditions is one of the arguments that the bromination of carbonyl compounds proceeds via the enol form. The formation of the enol form of camphorquinone is impossible since Bredt's rule would be violated. The fact that camphorquinone is incapable of deutero-exchange is accounted for in the same way (89).

The steric hindrances to the formation of a double bond at the bridgehead position decrease with increasing size of the ring. In the later 1940's Prelog (90) was engaged in checking up the possibility of existence of large rings with a double bond at the bridgehead. He established that Bredt's rule becomes invalid for systems in which the six-membered ring has a bridge at the 1,3-positions, which contains at least five carbon atoms. Prelog came to this conclusion by studying the direction of the croton condensation of compounds of the type XXXIX. In these compounds, an intramolecular croton condensation may take place, involving the formation of a condensed-ring structure (pathway A) or, provided this is not restricted by Bredt's rule, with the formation of a bridged structure with a double bond at the bridgehead position (pathway B):




XXXIX

The route B becomes more preferred with increasing $n$, as shown by the following figures:

| n | Yield of product by path A, % | Yield of product by path B, % |
|---|---|---|
| 4 | 65 | 0 |
| 5 | 32 | 14 |
| 6 | 0 | 76 |

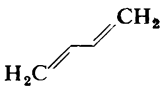
Later, Wiseman (91) proposed another criterion for determination of the range of applicability of the Bredt rule. He maintains that bicyclic compounds with a double bond at the bridgehead atom become capable of existence if the larger of the two rings, containing a double bond, has at least eight atoms in the ring. Wiseman attributes this to the fact that with this number of members in the ring the existence of *trans*-cycloal-

kenes becomes possible; it is such a fragment that must be a constituent part of a bridged structure. In accordance with this conception, it has been found possible to synthesize bicyclo[3.3.1]-1-nonene.

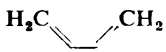
Compounds that exist in contrary to Bredt's rule are described by Köbrich (92). For the present-day interpretation of the Bredt rule, the reader is referred to the literature (93). An older review is also available (94).

## 6.8. STEREOCHEMISTRY OF CONJUGATED DIENES AND THEIR ANALOGUES

The conjugation of double bonds in 1,3-butadiene and analogous compounds is possible only in those cases where the molecule has a planar configuration. There may be two such conformations that differ by the rotation about the central C—C bond:



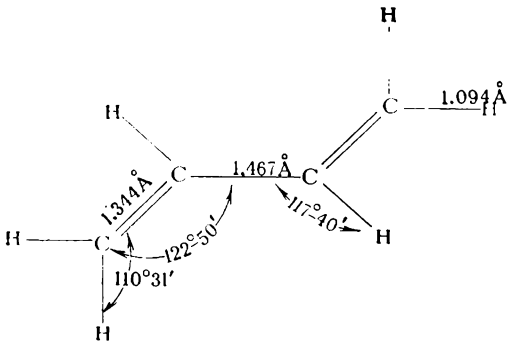
*s-trans*



*s-cis*

The designations *s-trans* and *s-cis* indicate the conformations about a single bond; they may also be termed the transoid and cisoid conformations, respectively.

In the simplest case of 1,3-butadiene, the *s-trans* conformation is more stable, whereas in the *s-cis* conformation there arise unfavourable interactions and the second relatively stable form is the skew conformation with a dihedral angle of about 35° (95). The rotational barrier separating the two conformations is equal to 20-30 kJ/mole (96). The geometric parameters of *s-trans*-1,3-butadiene (97) are given below:



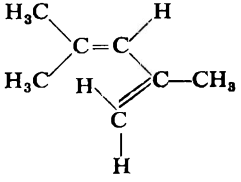
In 2,3-dimethyl-1,3-butadiene, the double-bond length is greater than in butadiene (1.36 Å instead of 1.34 Å); this prevents an increase of the strain in the system (98). The skew conformation with a dihedral angle of 42-48° has been found to be more favourable for hexafluoro-1,3-butadiene (99).

The energy preferableness of the transoid form is responsible for the fact that conjugated acyclic dienes exist predominantly in this conformation. On the other hand, monocyclic dienes may exist only in a configuration (it is precisely this term that must be used here!) corresponding to the *s-cis* conformation. The two conformations differ appreciably in UV spectra (Table 6.4).

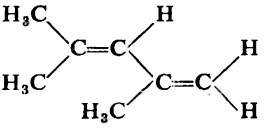
TABLE 6.4. ULTRAVIOLET SPECTRAL CHARACTERISTICS OF THE *s-cis*- AND *s-trans*-CONJUGATED DIENES

| | Compound | $\lambda_{max}$, nm | $\varepsilon$ |
|---|---|---|---|
| *s-trans*- | 1,3-Butadiene | 217 | 21,000 |
| | Isoprene | 220 | 24,000 |
| | 2,3-Dimethyl-1,3-butadiene | 241 | 23,000 |
| *s-cis*- | 1,3-Cyclopentadiene | 239 | 3,400 |
| | 1,3-Cyclohexadiene | 256 | 8,000 |
| | 1,2-Dimethylidenecyclohexane | 220 | 10,000 |

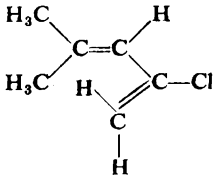
The data listed in Table 6.4 indicate that the *position* of the absorption maximum does not show characteristic differences for the *s-trans*- and *s-cis*-forms, but the absorption intensity for the *s-cis*-form is substantially lower than for the *s-trans*-form. Based on this difference, one can often determine the position of double bonds in complex polycyclic structures (steroids, triterpenes) and also in acyclic dienes with a branched carbon skeleton (100). As an example may be cited 1,1,3-trimethyl-1,3-butadiene which, according to its UV spectrum ($\lambda_{max} = 228$ nm and $\varepsilon = 8{,}500$), exists in the *s-cis* conformation because in the *s-trans* conformation the methyl groups undergo undesired interactions:



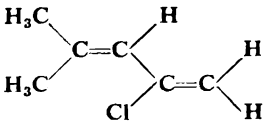
*s-cis*-



*s-trans*-



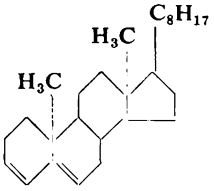
*s-cis-*



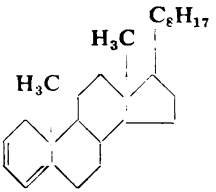
*s-trans-*

3-Chloro-1,1-dimethyl-1,3-butadiene shows $\lambda_{max} = 233$ nm and $\varepsilon = 8{,}100$ in its UV spectrum; in this compound, either of the forms, *s-cis-* and *s-trans-*, cannot be realized because of the overlap of the substituents. Therefore, the molecule exists in the skew (along the central bond) conformation. It is the decreased conjugation caused by this conformation that leads to a fall in the intensity of UV absorption as compared with unsubstituted 1,3-butadiene.

As previously mentioned, such spectral differences assumed special importance in studying polycyclic dienes. These compounds may contain both double bonds either in one and the same ring **(homoannular dienes)** and will invariably have the *s-cis*-form, or in different rings **(heteroannular dienes)**.

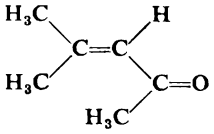


3,5-Cholestadiene
*s-trans-*, ε 23,000

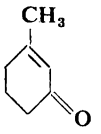


2,4-Cholestadiene
*s-cis-*, ε 6,500

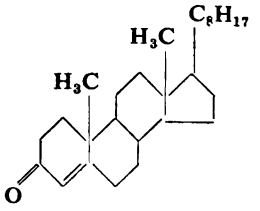
The intensity of the absorption band in the region of 220-240 nm allows us to differentiate clearly between homoannular and heteroannular conjugated dienes. Analogous differences in UV spectra are observed also for α,β-unsaturated ketones:



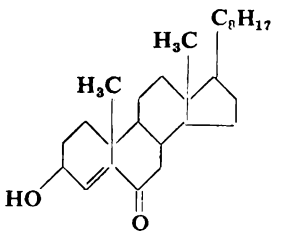
Mesityl oxide
*s-trans-*, ε 14,000



1-Methyl-3-cyclohexenone
*s-trans-*, ε 12,950

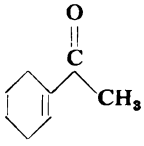


4-Cholesten-3-one
*s-trans*-, ε 19,950

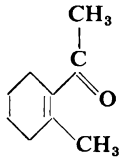


3-Hydroxy-4-cholesten-6-one
*s-cis*-, ε 6,300

Ultraviolet spectra can also be used for determination of the conformations of conformationally mobile α,β-unsaturated ketones. They enable us to establish, for example, that whereas 1-acetyl-1-cyclohexene exists in the *s-trans* conformation, its homologue, 2-methyl-1-acetyl-1-cyclohexene adopts the *s-cis* conformation since in the *s-trans* conformation there would arise an unfavourable interaction between the two methyl groups:

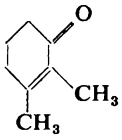


1-Acetyl-1-cyclohexene
*s-trans*-, ε 12,400

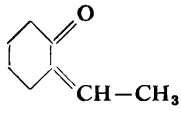


2-Methyl-1-acetyl-1-cyclohexene, *s-cis*-, ε 6,890

Infrared spectra too may be employed for a conformational study of conjugated unsaturated ketones. The following compounds have been used by Dutch chemists (101) as standards with a fixed spatial arrangement of the enonic system:



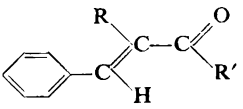
2,3-Dimethyl-2-cyclohexen-1-one
$\nu_{CO}$ = 1673 cm$^{-1}$



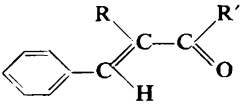
2-Ethylidenecyclohexanone
$\nu_{CO}$ = 1693 cm$^{-1}$

A comparison of the frequencies of stretching vibrations of the CO group in conformationally flexible compounds — *trans*-benzalacetone

(*trans*-benzilideneacetone) and its homologues—has made it possible to draw conclusions as to their conformations:



*s-trans-*



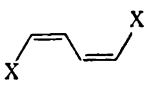
*s-cis-*

The IR spectra of compounds of the same type

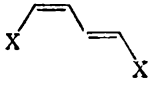
$$C_6H_5—CH=CH—CO—CH_2R$$

have been examined in the literature (102).

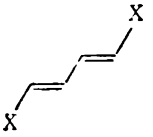
The studies of 1,4-dihalogeno-1,3-butadienes carried out by Viehe and Franchimont (103) are concerned not with conformers but with the position of the thermodynamic equilibrium involving three possible stable (individual) geometric isomers. In benzene solution at 100°C in the presence of 1 per cent of iodine the thermodynamic equilibrium sets in with the following content of the separate spatial forms:



*cis-cis-*
X = F 43%
X = Cl 51%



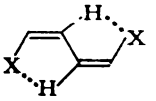
*cis-trans-*
43%
40%



*trans-trans-*
14%
9%

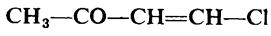
The same preferableness of the *cis*-forms has been observed for 1-halogeno-1,3-butadienes of the general formula X—CH=CH—CH=$CH_2$. With X=F the content of the *cis*-form at the thermodynamical equilibrium is 62 per cent; with X=Cl, the content of the *cis*-form in the equilibrium mixture is even higher: 70 per cent. The authors believe that the *s-trans* conformation is the most stable conformation for 1,4-dihalogenobutadienes:

X—CH=CH—CH=CH—X

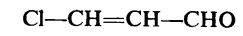


assuming that in this conformation there is an attraction between the halogen and hydrogen atoms. Such a conformation had been proposed earlier by M.I. Batuev (104) for the mono-halogen analogue, 1-chloro-1,3-butadiene.

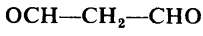
The conformation about the central C—C bond has also been studied for a number of other unsaturated carbonyl compounds: methyl-β-chlorovinyl ketone XL, β-chloroacrolein XLI, malondialdehyde XLII and its methyl homologue XLIII; these investigations were carried out with the aid of the NMR method (105).



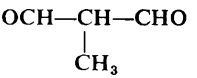
XL



XLI

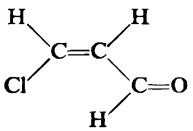


XLII

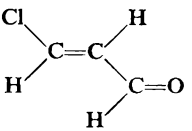


XLIII

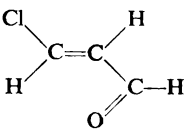
All these molecules are flat; *cis*-β-chloroacrolein has the *s-trans* conformation XLIa and in the *trans*-isomer the two conformations XLIb and XLIb′ are evidently in equilibrium:



XLIa

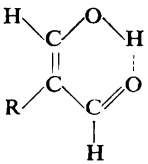


XLIb



XLIb′

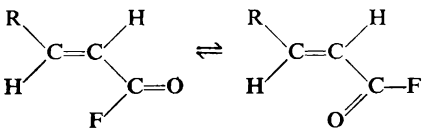
Malondialdehyde and its methyl homologue exist in the enol form, in which the *s-cis* conformation is fixed by an intramolecular hydrogen bond:



XLIIa (R=H)

XLIIIa ($R=CH_3$)

Diverse material is available in the literature on the conformations about the central carbon-carbon single bond in α,β-unsaturated carboxylic acids and their derivatives (106); for example:

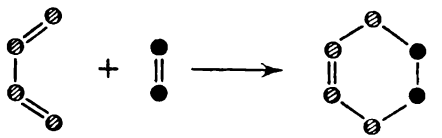


*s-trans-* *s-cis-*

We shall not discuss in detail the stereochemistry of the reactions of dienes and α,β-unsaturated carbonyl compounds; the reader is referred to the work of Hautala *et al.* (107).

## 6.9. STEREOCHEMISTRY OF DIENE SYNTHESIS

The reactions of 1,4-addition of compounds with an activated double or triple bond **(dienophiles)** to conjugated dienes are known as the **diene synthesis.** This synthesis is often termed the Diels-Alder reaction after the names of the scientists who discovered this peculiar conversion in 1928 (108). This reaction in its most general form may be depicted by the following scheme:

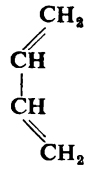


Diene Dienophile Adduct

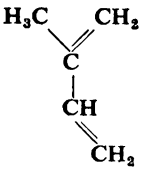
The various carbocyclic and heterocyclic systems with six-membered rings—mono- and polycyclic and bridged systems—can be easily prepared by means of the Diels-Alder reaction (diene synthesis). Diene synthesis is highly interesting from the stereochemical standpoint. Strict steric requirements are put forth to starting compounds, and the spatial structure of the adducts obtained obey definite rules. Only dienes in the *s-cis* conformations enter into a Diels-Alder reaction. This conformation is present in cyclic dienes; it can be adopted by butadiene and its analogues with an unbranched carbon chain. But if there are side chains, the possibility of creation of the *s-cis* conformation in acyclic compounds is strongly dependent on the nature of the substituents and on the geometrical *(cis-trans)* configuration.

In the light of what has been said, the following compounds are active dienes (154):

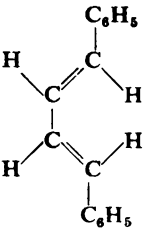
Cyclopentadiene 1,3-Cyclohexadiene Furan



1,3-Butadiene

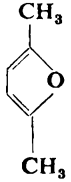


Isoprene

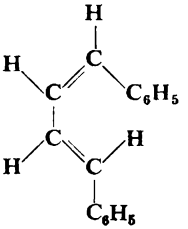


*trans-trans*-1,4-Diphenyl-1,3-butadiene

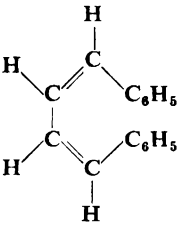
The following are slightly active dienes:



2,5-Dimethylfuran



*cis-trans*-1,4-Diphenyl-1,3-butadiene

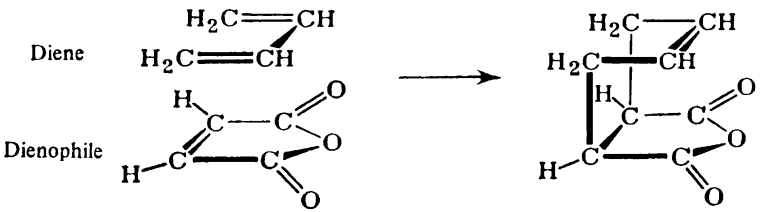


*cis-cis*-1,4-Diphenyl-1,3-butadiene

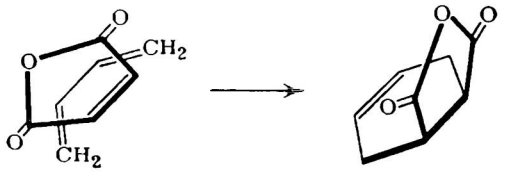
The low activity of the last two compounds is associated with steric difficulties arising during the development of the *s-cis* conformation. The effect of the structure of dienes on their reactivity in diene synthesis has been discussed in the literature (109).

The result of the diene synthesis is influenced to no less an extent by the second participant of the reaction—the dienophile. The role of the dienophile is most frequently played by maleic anhydride, but many other compounds of the type $CH_2{=}CH{-}X$, where X=electron-accepting group (CHO, COR, COOR, CN) which activates the carbon-carbon double bond of the dienophile, are in general also suitable for the purpose. For a discussion of the various dienophiles, the reader is referred to the literature (110).

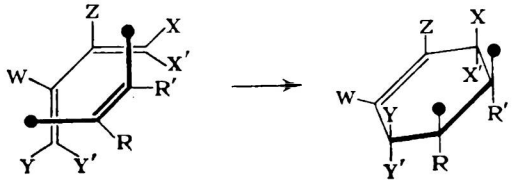
The steric course of diene synthesis is most spectacularly revealed through the use of perspective formulas in which a diene is shown to lie above the dienophile molecule. For example:



Alder proposed replacing the perspective representation by a conventional planar one in which the transient complex is viewed as if from below, from the side of the dienophile. In the example given above this would look as follows:



Or, in a general case (157):



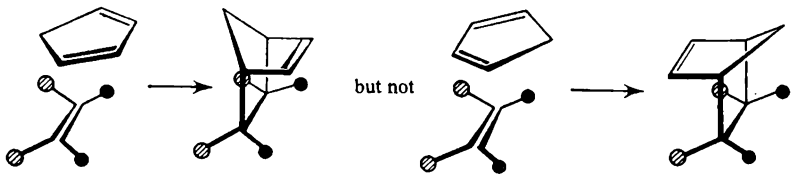
The regularities that govern the stereochemical course of diene synthesis were first established for cyclic dienes and later extended to dienes of acyclic structure. In their most general form these regularities may be expressed thus: a diene reacts by the mechanism of 1,4-addition in the *s-cis* conformation, adding on to the dienophile in *cis* fashion. The adduct formed retains the stereochemical features of the diene and the dienophile.

In a more concrete form, this is expressed by the following rules.

1. The *cis*-addition rule: diene synthesis proceeds by the scheme of *cis*-addition of a diene to a dienophile:

2. The rule of maximum accumulation of double bonds: in the transient reaction complex the diene and dienophile molecules are oriented in such a way that the double bonds of the diene are very close to the

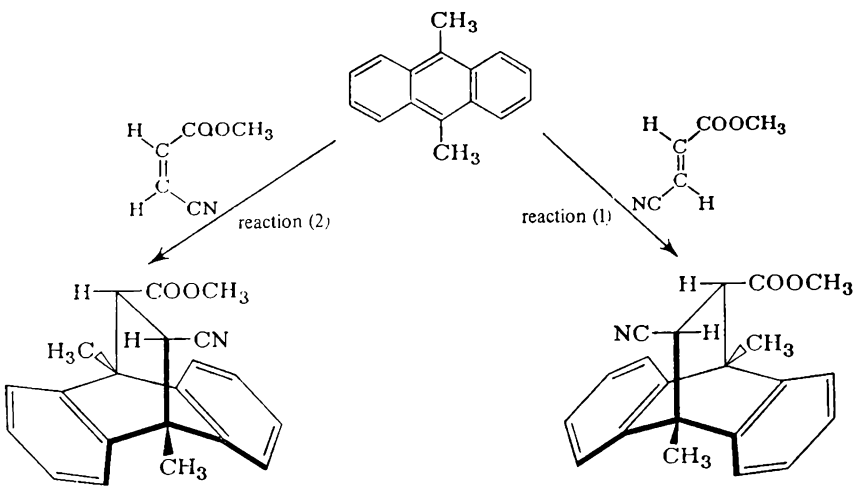
unsaturated activating groups of the dienophile (these groups are represented by filled circles):




The rule of maximum accumulation of double bonds may also be formulated in a different manner: the configuration of the resulting adduct is determined by the tendency of the double bond formed in it to arrange itself in space as near to the activating group as possible.

In a special case of the formation of bicyclic compounds of the bornane type, this rule leads to the following: the unsaturated activating group of the dienophile invariably occupies the *endo*-position in the adduct. Hence the other name of this rule—the **Alder endo rule**, or simply the Alder rule.

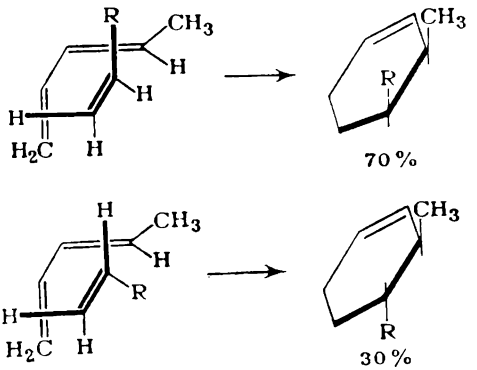
The rule of *cis*-addition with retention of the configuration of the compounds involved may be illustrated by using the following example:




Yield 100% Yield 98%

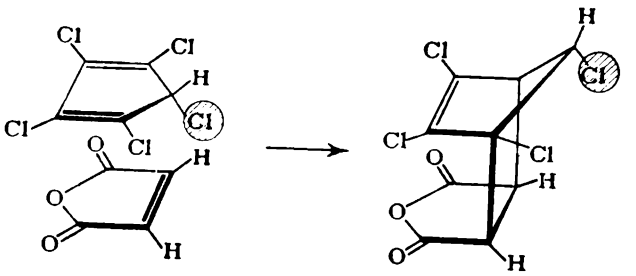
The adduct formed from a dienophile having the *trans*-configuration (reaction 1) retains the *trans*-arrangement; the adduct resulting from a dienophile with the *cis*-configuration (reaction 2) retains the *cis*-arrangement of the substituents at the six-membered ring formed.

*trans*-Piperylene reacts analogously with acrylic acid or acrolein. In this case, depending on the orientation, in accordance with or contrary to the rule of maximum accumulation of double bonds, two isomeric compounds are formed (the isomer that obeys the rule predominates). We shall make use of the Alder method for writing the schemes for the two directions of the reaction. A comparison with the representation of the preceding reactions will show that this method is more spectacular for acyclic dienes (R = COOH in the reaction with acrylic acid and R = CHO in the reaction with acrolein):

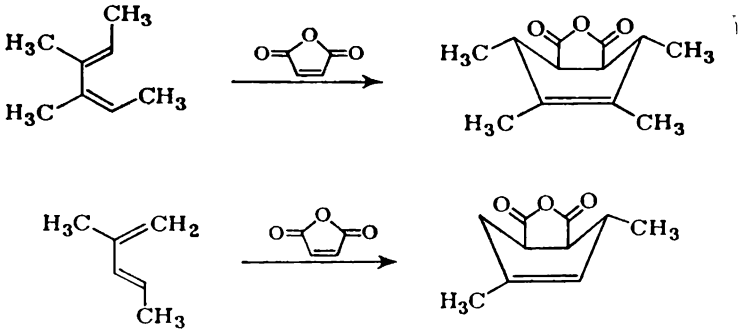



The stereochemistry of the Diels-Alder reaction involving isoprene and cinnamaldehyde (or cinnamic acid) has been studied (111).

The use of cyclopentadiene derivatives with a monosubstituted methylene group as a diene provides a further possibility for spatial isomerism: the substituent in the adduct formed may be either brought closer to the double bond (*syn*-orientation) or taken away from it (*anti*-orientation). An investigation of the reaction between pentachlorocyclopentadiene and maleic anhydride from this standpoint has shown that 91-99 per cent of the *anti*-isomer is formed, which requires, it would seem, an unfavourable arrangement of chlorine in the transition state complex (112):



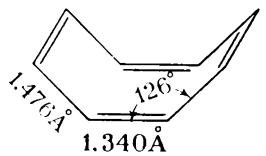
Diene syntheses involving highly substituted dienes may lead to the building of structures in which the cyclohexane ring has the boat conformation; for example (113):



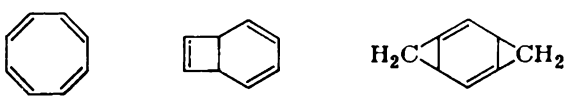
For a discussion of the mechanism and stereochemistry of diene synthesis, the reader is referred to the review article written by Sauer (114). A critical review of the older data on the stereochemistry of the reaction was written by Martin and Hill (115).

## 6.10. STEREOISOMERISM OF CYCLOOCTATETRAENE

The geometric form of cyclooctatetraene has been elucidated by means of the electron diffraction method in the gas phase (116). This compound exists in a boat-shaped conformation with the following parameters:

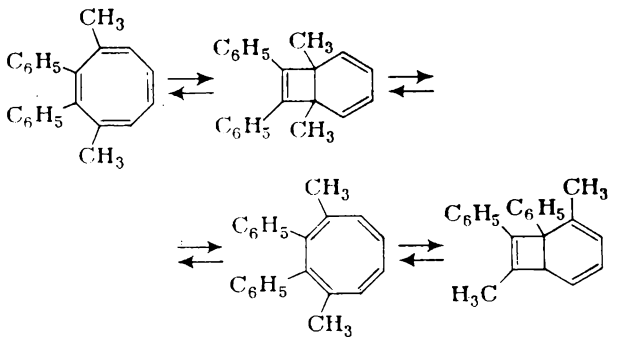



Many of the conversions of cyclooctatetraene are accompanied by rearrangements of the carbon skeleton. Cyclooctatetraene behaves in these reactions as if it were an equilibrium mixture of the three forms XLIVa, XLIVb, and XLIVc, one of these forms participating predominantly in this or that reaction:



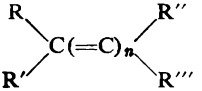
XLIVa XLIVb XLIVc

The fact that the rate of the reaction of cyclooctatetraene with maleic anhydride is independent of the concentration of the latter has been interpreted from the standpoint of such an equilibrium: the reaction involves the valence isomer XLIVb, the rate of formation of which evidently limits the rate of the overall reaction (117). In the case of a substituted cyclooctatetraene, the existence of several isomeric forms has been proved by means of the NMR method (118):

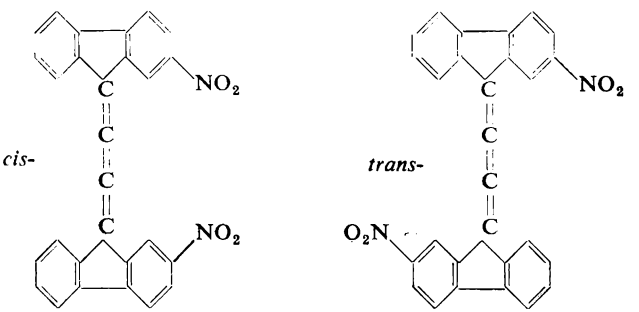


## 6.11. STEREOISOMERISM OF THE CUMULENES

Cumulenes are compounds with several adjacent (cumulated) double bonds. Their structure may be represented by the general formula:

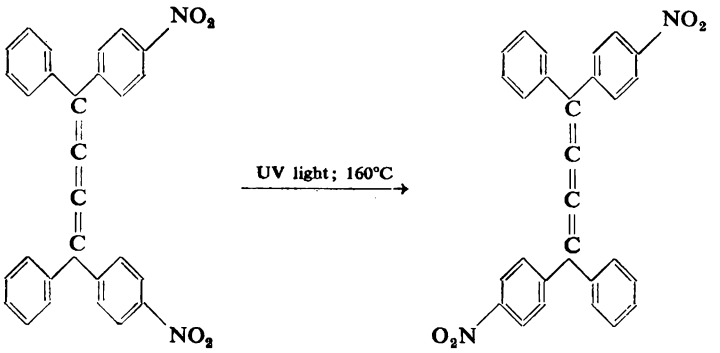


Depending on the number of cumulated double bonds, compounds of this type may exhibit either geometrical or optical isomerism. The geometrical *(cis-trans)* isomerism of cumulenes is manifested with any *odd* number of cumulated double bonds. The simplest case with $n = 1$ is the *cis-trans* isomerism of ethylene hydrocarbons. Geometrically isomeric cumulenes with $n = 3$ and 5 are also known:



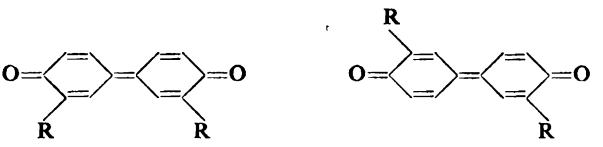
Kuhn separated these *cis*- and *trans*-isomers by means of chromatographic techniques using aluminium oxide.

In compound XLV, the butatriene system is not linked to the ring and is purely aliphatic. The two forms differ significantly in dipole moment: the *cis*-form has a dipole moment of 7 D, and the *trans*-form, only 1.9 D.




XLVa XLVE

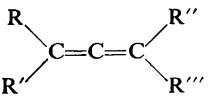
A peculiar type of *cis-trans* isomerism may arise in systems of the diphenoquinone type:




*cis*-Form *trans*-Form

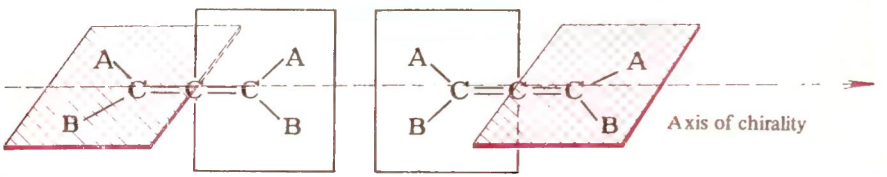
Compounds of this kind have been studied, for example, by Kessler and Rieker (119).

Cumulenes with any *even* number of cumulated double bonds display optical isomerism. The most thoroughly studied cumulenes of this type are the **allenes,** i.e., compounds having the following structure:

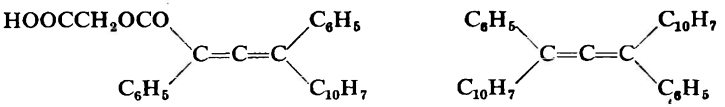



The possibility of existence of optically active allenes was predicted by van't Hoff in 1877 on the basis of the hypothesis of the tetrahedral carbon atom. At present, optically active allenes are regarded as com-

pounds with an *axis of chirality* (in contrast to compounds with an asymmetric atom—a *chiral centre*):

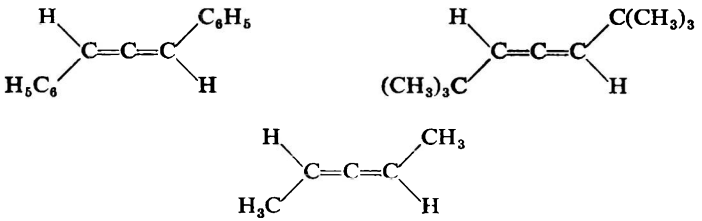



Allenes were unknown at the time of van't Hoff. The first optically active allenes were prepared by Kohler only in the 1930's.

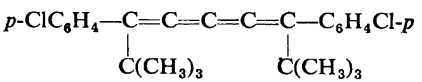



These allenes contain 3 or 4 aromatic substituents, as a result of which their stability increases and the tendency towards polymerization is reduced. Optically active allenes are very stable. They are not racemized even on prolonged heating at 190°C in decalin. The stability of optical antipodes (enantiomers) of the allene type is in agreement with the high barrier to internal rotation in such compounds (120). The rotational barrier for allene is 305 kJ/mole.

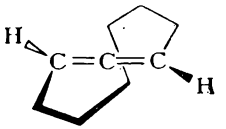
As the data on the properties and routes of synthesis of allenes accumulated it became possible to prepare simpler allenes that had been considered earlier to be unstable. Some of them were obtained in an optically active form, say, 1,3-diphenylallene (121), 1,3-di-*tert*-butylallene (122), 2,3-pentadiene (123):




Optically active higher cumulenes are also known to exist (124):



An interesting cyclic allene is 1,2-cyclononadiene, which has been also obtained in an optically active form (125):

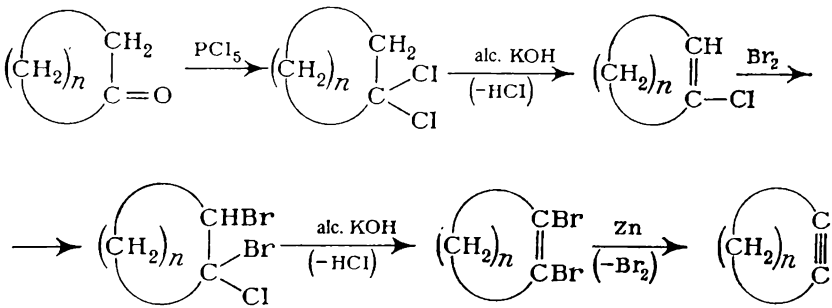


(+) -

## 6.12. STEREOCHEMISTRY OF THE CYCLOALKYNES

The four carbon atoms in the C—C≡C—C system lie on a single straight line; it is obvious that such a "rigid rod" is difficult to visualize as being a constituent part of a ring with a small number of members. The attempts to establish the minimum size of the ring that makes possible the existence of cycloalkynes have long been made. The first unsuccessful attempts undertaken by Markovnikov, Willstatter, and Favorsky were followed by the successful preparation effected by Domnin (126) in the thirties of this century.

To prepare **cyclooctyne,** Domnin made use of the scheme developed by Favorsky and employed unsuccessfully for smaller rings ($n$ = 3, 4, 5).

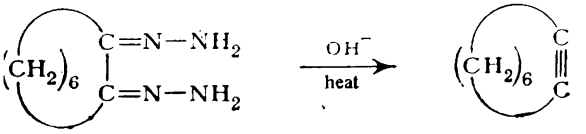



When cyclooctanone ($n$ = 6) was used as the starting compound, the hydrocarbon $C_8H_{12}$ was isolated, which on oxidation gave suberic acid, $HOOC(CH_2)_6COOH$, this being an indication of the presence of cyclooctyne. When at a later time the Domnin cyclooctyne was subjected to spectral analysis (127), it was found that the Raman spectrum shows a double-bond line along with the triple-bond line (2112 $cm^{-1}$).

At least nine compounds were detected in the Domnin cyclooctyne by means of gas-liquid chromatography, NMR and mass spectrometry.

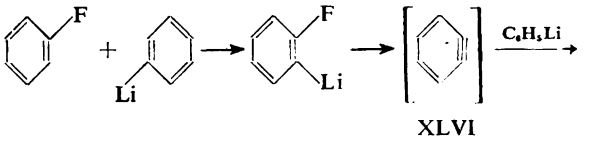
The main conclusion made by Domnin as to the possibility of existence of an eight-membered ring with a triple bond was however correct and was supported when Blomquist (129) obtained pure cyclooctyne

(b.p. 157.5-158°C at 740 mm Hg; $n_D^{20} = 1.4850$; $d_4^{20} = 0.868$) by a different route:

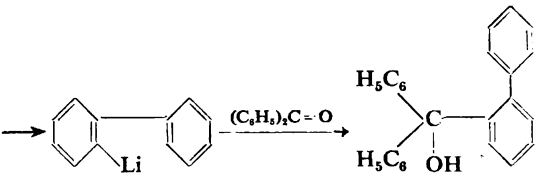



The introduction of a triple bond into rings with a larger number of members must no longer present difficulties; this was confirmed experimentally in the 1930's in the works of Ruzicka.

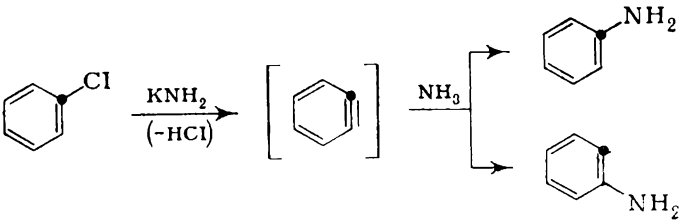
A new, extremely interesting page in the field of rings with a triple bond was opened by the works of Wittig (130). In 1948, Wittig observed the anomalous behaviour of fluorobenzene in the reaction with phenyllithium and explained the results obtained by the intermediate formation of **dehydrobenzene** XLVI, a six-membered ring with two double bonds and one carbon-carbon triple bond:



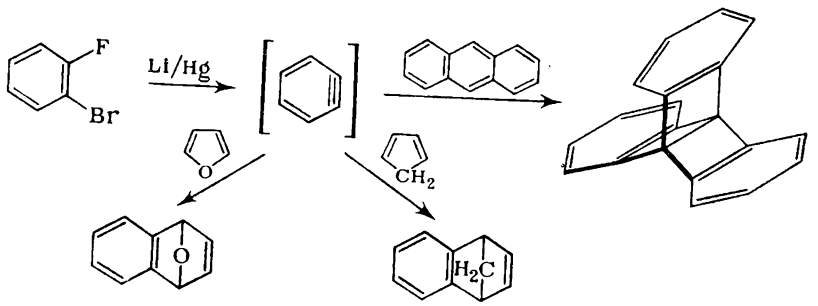

XLVI




Later, the conclusion as to the intermediate formation of dehydrobenzene was also made by Roberts, who established that in the reaction of potassamide with ring-labelled chlorobenzene the amino group becomes attached not only to the atom to which the chlorine was linked but is found, with equal probability, to be linked to the adjacent carbon atom:

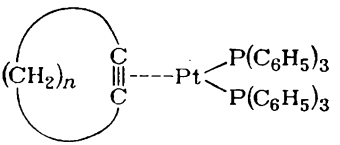


A direct proof of the short-time existence of dehydrobenzene was its "being trapped" as a reactive dienophile in the Diels-Alder reaction. Wittig used furan, cyclopentadiene, or anthracene as the diene:



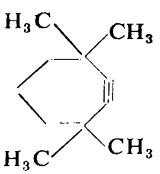

It is interesting that the reaction with anthracene makes it possible to easily prepare a polycyclic hydrocarbon, triptycene; no convenient routes for the synthesis of this compound has been known.

Using the "trapping" method, Wittig also proved the short-life existence of cyclopentyne, cyclohexyne, and cycloheptyne. Cycloalkynes have also been stabilized in the form of complexes with platinum, for example (131):

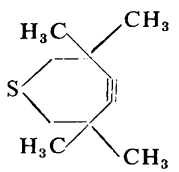



The X-ray diffraction study of the cycloheptyne complex has shown that the cycloheptyne ring in it has the twist-chair conformation, and that the entire complex is built as pictured in Fig. 6.3.

The introduction of substituents into the cycloalkyne ring increases its stability. Thus, 3,3,7,7-tetramethylcycloheptyne XLVII can be prepared in the free state, though it is rather unstable and is readily polymerized (132). Its heterocyclic analogue XLVII is even more stable: it is stable even at 140°C (133).

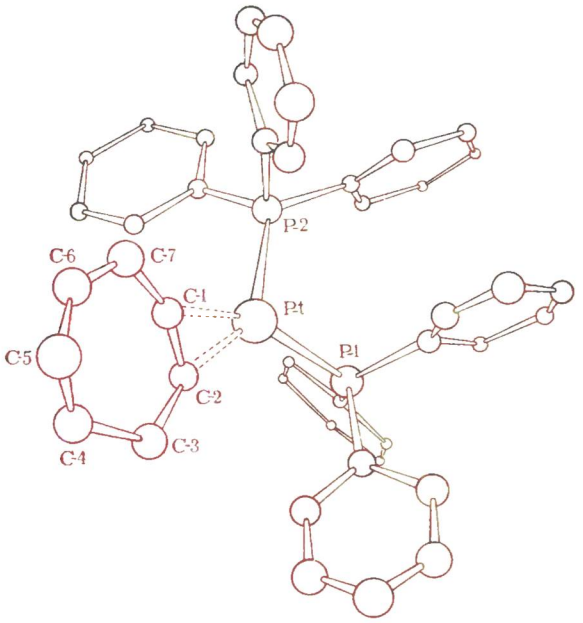



XLVII




XLVIII

Figure 6.3.

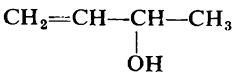



*The structure of a complex of cycloheptyne with platinum according to X-ray diffraction data.*

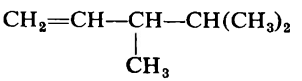
## 6.13. OPTICAL ACTIVITY OF UNSATURATED COMPOUNDS

In the various sections of this chapter, mention has been repeatedly made of optically active compounds—cyclooctene, allenes, etc. Apart from these, rather "exotic" examples, optical activity can be observed in ordinary unsaturated compounds with a usual asymmetric carbon atom. These substances do not differ at all in chiral-optical properties from the other optically active compounds that have been considered in Chapters 4 and 5. The absorption band of an isolated double bond, which is in the far-ultraviolet region of the spectrum, does not by itself cause the Cotton effect in the region accessible for ordinary measurements. Having obtained charge-transfer complexes from olefins, one can however observe the optical activity of the absorption band that appears in this process (134).

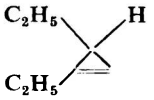
Below are given some of the optically active structures of this type, taken at random from a large number of such compounds:



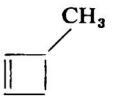
1-Buten-3-ol (135)



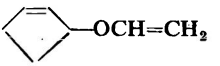
3,4-Dimethyl-1-pentene (136)



1,3-Diethyl-cyclopropene (137)



3-Methyl-cyclobutene (138)

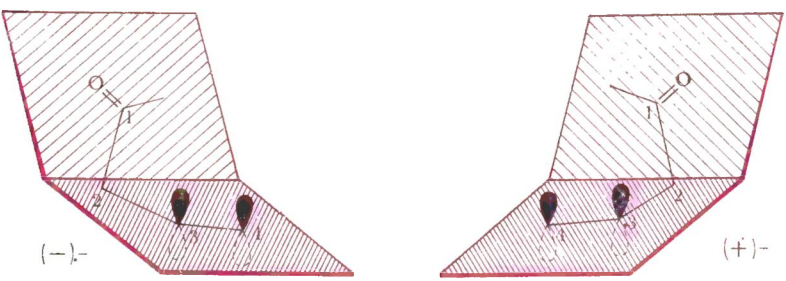


Vinyl ester of 1-cyclopenten-3-ol (139)

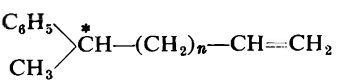
Many unsaturated optically active compounds belong to the class of terpenes and steroids.

Interesting features are displayed by optically active dienes: here the diene system plays the role of an "inherently asymmetric chromophore" (140) (Fig. 6.4).

This refers not only to 1,3-dienes, α,β-unsaturated ketones (i.e., conjugated systems) but also to β,γ-unsaturated ketones. The sign of rotation of the last-named compounds in rigid cyclic systems is entirely determined by the configuration of the inherently asymmetric homoconjugated chromophore.

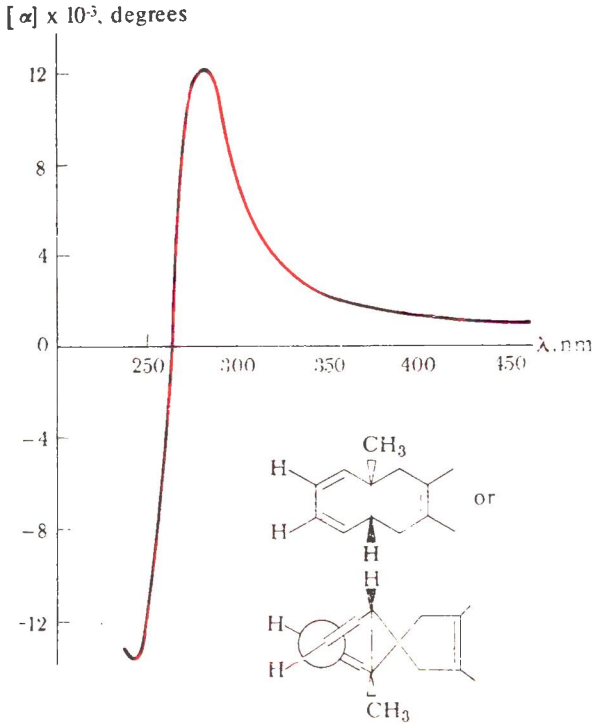



The homoconjugation of the phenyl group and the double bond is also manifested in the chiral-optical properties of phenylolefins of the type XLIX (142) and other compounds (143).



XLIX

Figure 6.4.




*The optical rotatory dispersion curve of the inherently asymmetric diene chromophore.*

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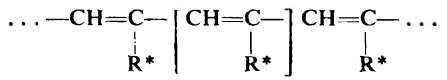
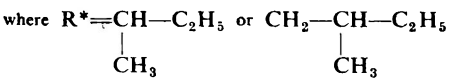
Optically active olefins have been used in many cases for the synthesis of other optically active compounds, say, aldehydes (by way of hydroformylation) (144), and unsaturated hydroxy acids (145).

The inherently asymmetric spiral chromophore also determines the optical rotation of a linear polyene containing an optically active radical in the side chain (146).

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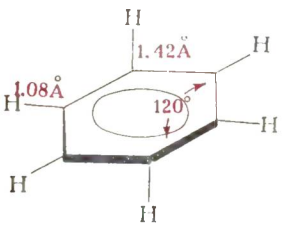
CHAPTER 7

# Stereochemistry of Aromatic Compounds

## 7.1. CONFORMATIONS OF SUBSTITUTED ARENES

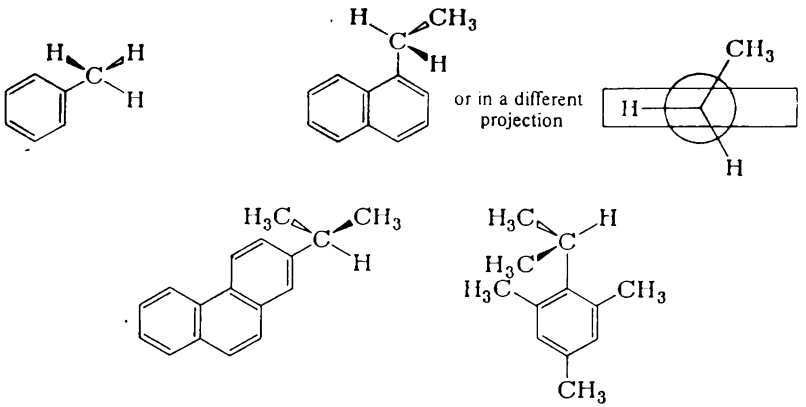
The basic structural unit of aromatic compounds, the benzene ring, is characterized by the following geometrical parameters:



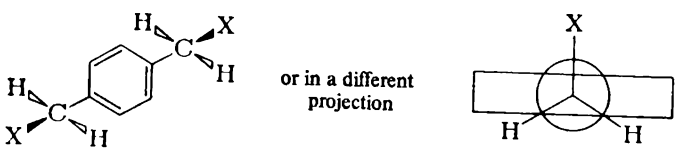

In a first approximation, the benzene molecule may be visualized as a disc having a diameter of about 5 Å and a thickness of the order of 2 Å. All the six C—H bonds are in the plane of the benzene ring. The same disposition must be taken by any other atoms directly linked to the benzene ring. The swinging out of the plane is associated with the appearance of a noticeable strain energy and renders the system less stable.

The rotation about the bond between the aromatic nucleus and the substituent gives rise to various conformations. The following material is available at present as to which of the conformations are more preferable. The study of the conformations of aromatic hydrocarbons with side chains (Ar—R) has shown that if R = methyl, ethyl or isopropyl

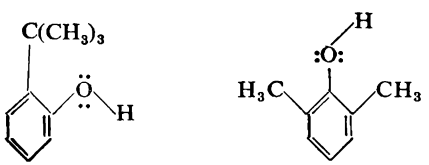
group, the C—H bond of the α-carbon atom in the preferred conformation is coplanar with the aromatic nucleus. If the substituents are very bulky (for example, the neopentyl group), their free rotation may become difficult (1).




In *p-bis*-(halogenomethyl)-benzenes the C—X bonds arrange themselves perpendicularly to the aromatic nucleus (2):

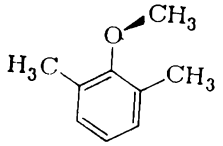



The hydroxyl group in phenols lies in the ring plane; even the neighbourhood of the *tert*-butyl group does not disturb this conformation:

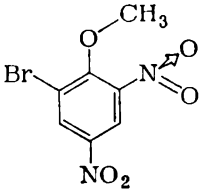


With this arrangement one of the free electron pairs on the oxygen atom is conjugated with the π-electron system of the benzene ring. In passing from 2,6-dimethylphenol to the corresponding ether the planar

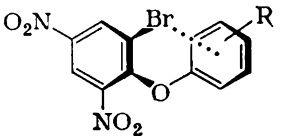
arrangement is no longer possible: the $OCH_3$ group becomes perpendicular to the plane of the benzene ring; the conjugation is thus disturbed (3):



If the methoxy group is adjacent to the nitro group, the former remains in the plane of the benzene ring and the latter turns perpendicularly to this plane (I); the signs of formation of charge-transfer complexes have been noted for substituted nitrodiphenyl esters II (4):

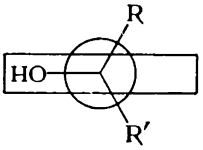


I

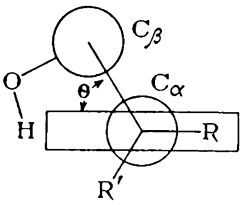


II

Phenylcarbinols (5) of the general formula $Ar—C(OH)R_2$ exist preferentially in conformations in which the hydroxyl group lies in the plane of the benzene ring (III); but if the OH group is in the β-position to the benzene ring (IV), then the signs of an intramolecular hydrogen bond between the hydroxyl group and the π-electron density of the benzene ring can be detected in the IR spectra (6).



III

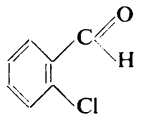


IV

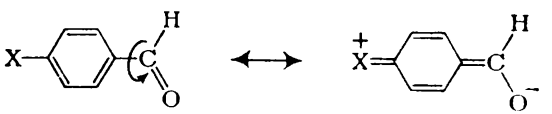
The observed position of the OH band in the IR spectrum can be calculated by the following formula:

$$\nu_{OH}\ cm^{-1} = 3625 - 50 \times \cos 2\ (\theta - 30°)$$

The most preferred conformation of the aldehyde group is the conjugation-stabilized planar form; *o*-chlorobenzaldehyde also exists preferentially in a planar form, the hydrogen atom of the aldehyde group being turned to the chlorine atom (7):



The height of the barrier to the rotation of the aldehyde group in *p*-substituted benzaldehydes is influenced by the nature of the substituent, which is a reflection of the contribution of the bipolar boundary structure (a structure with charge separation) (8).



The barrier height correlates with the Hammett induction constants:

| Substituent X | $(CH_3)_2N$ | $OCH_3$ | OH | H |
|---|---|---|---|---|
| Barrier, kJ/mole | 96 | 36 | 29 | 28 |
| $\sigma$ | −0.44 | −0.12 | −0.13 | 0 |

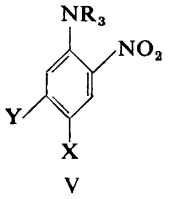
The protonation of the aldehyde group (by the action of $SbF_5$ + + $FSO_3H$) increases the contribution of the bipolar boundary structure and increases the rotational barrier up to 63-67 kJ/mole (8).

Salicylaldehyde exists in a planar conformation with an intramolecular hydrogen bond; the presence of two forms has been revealed in 3-nitrosalicylaldehyde according to dipole moment data: in one of them the hydroxyl group is linked to the aldehyde group through a hydrogen bond and in the other, to the nitro group (10).

The dimethylamino group tends to adopt a conformation capable of providing an energy gain owing to the conjugation of the free electron pair on the nitrogen atom with the aromatic nucleus; the methyl groups arrange themselves in the plane of the ring (11). Just as in substituted benzaldehydes, the rotational barrier depends on the nature and position of the substituents (12). Its height varies from 21 kJ/mole (unsubstituted dimethylaniline) to 67 kJ/mole (2,4-dinitro-N,N-dimethylaniline).

In *o*-nitroanilines of the general formula V, the additional groups introduced at the *p*-position relative to one of the groups present can contrib-

ute to the fixing of this group in the plane of the benzene ring due to the mesomeric effect; then the second group which has received no "electron support" is forced to turn perpendicularly to the ring (13).



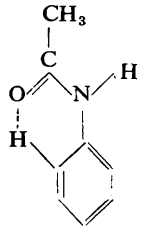

V

R = H, $CH_3$

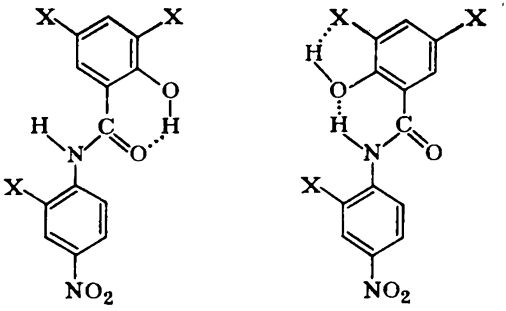
X = H, $NO_2$

Y = H, $N(CH_3)_2$

In compounds of the acetanilide type, the substituent is found to lie in the plane of the benzene ring, a hydrogen bond being formed between the CO group and the hydrogen in the *ortho*-position (14):

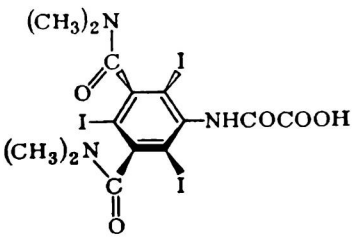



Substituted salicylanilides exist in two crystalline modifications which differ by the nature of the intramolecular hydrogen bonds (15):

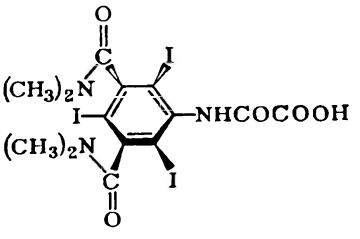



Interesting results have been obtained in an investigation of the substituted amides of *m*-phthalic acid. The iodine atoms make the dimethylamide groups turn perpendicularly to the benzene ring, which leads to

the existence of two geometrically isomeric forms: the *cis*-isomer, m.p. 204-209°C, $R_f = 0.33$ (over silica gel) and the *trans*-isomer, m.p. 201-211°C, $R_f = 0.40$ (over silica gel):




*cis*-




*trans*-

The configuration of the *trans*-isomer has been confirmed by its resolution into optical antipodes via the brucine salt (16).

## 7.2. SHIELDING OF ORTHO-POSITIONS

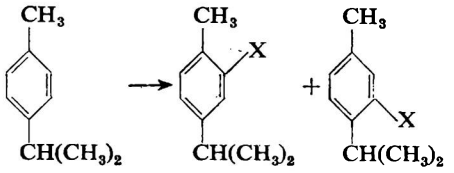
Bulky substituents linked to the benzene ring shield the adjacent positions in the ring and make the introduction of substituents at these positions less favourable. Effects of this kind have been observed in the nitration of alkylbenzenes: the fraction of the *ortho*-isomer formed decreases with increasing size of the alkyl group:

| Alkylbenzene | The *ortho*:*para* isomers ratio |
|---|---|
| Toluene | 1.57 |
| Ethylbenzene | 0.93 |
| Isopropylbenzene (cumene) | 0.48 |
| *tert*-Butylbenzene | 0.22 |

Analogous results have been obtained for nitration, chlorination, bromination, and chloromethylation (17).

Steric effects also control the entry of substituents into *p*-dialkylbenzenes containing *different* alkyl groups: the substituent enters preferentially the *ortho*-position relative to the *smaller* of the two alkyl groups.

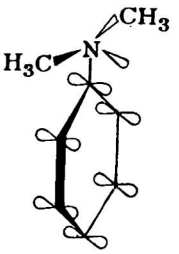
This may be illustrated by data on the orientation of electrophilic substitution reactions in *p*-cymene (*p*-isopropylmethylbenzene):




| Reaction | X | Per cent fraction of isomers | |
|---|---|---|---|
| Bromination | Br | 54 | 46 |
| Chlorination | Cl | 59 | 41 |
| Nitration | $NO_2$ | 70 | 30 |
| Sulphonation | $SO_3H$ | 89 | 11 |

## 7.3. STERIC BREAK IN CONJUGATION

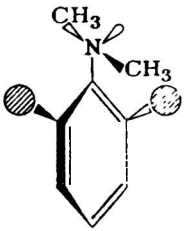
It is well known that the aromatic nucleus has a significant effect on the properties of the amino group attached to it (the weakening of the basic properties of aniline as compared with aliphatic amines), and the amino group in its turn exerts an influence on the properties of the aromatic ring. This is a consequence of the conjugation of the free electron pair on nitrogen with the mobile π-electrons of the aromatic nucleus. Conjugation may occur only with the parallel orientation of the *p*-electron orbital of the electron pair on nitrogen and the π-electron system of the aromatic nucleus:



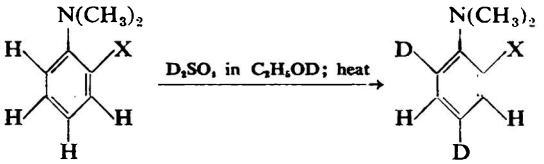

Because of this, as has already been mentioned, in dimethylaniline the $CH_3$ groups lie in the ring plane, and the *p*-orbital of the free electron

pair on nitrogen is perpendicular to the plane of the ring, i.e., parallel to the π-electron system of the aromatic ring.

With the appearance of bulky substituents in the *ortho*-position such a conformation becomes unfavourable (the overlap of the van der Waals radii of the $CH_3$ groups of the dimethylamino group and the *ortho*-substituents), and the dimethylamino group has to turn so that a break in conjugation occurs:



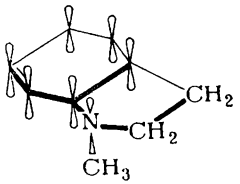
The break in conjugation causes a decrease of the activating effect of the amino group on the aromatic ring. This has been traced out, for example, in the following deuterium-exchange reaction:



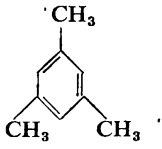

Steric hindrances to conjugation increase with increasing size of *ortho*-substituents X and the exchange for deuterium becomes increasingly less pronounced:

| Compound | Number of hydrogen atoms exchanged for deuterium per one mole of substance |
|---|---|
| N,N-Dimethylaniline | 1.73 |
| 2-Fluoro-N,N-dimethylaniline | 0.96 |
| 2-Chloro-N,N-dimethylaniline | 0.05 |
| 2-Bromo-N,N-dimethylaniline | 0.02 |
| 2-Methyl-N,N-dimethylaniline | 0 |
| N-Methylindoline | 1.58 |

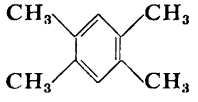
The special activity of N-methylindoline is accounted for by the fact that it has a five-membered ring which provides a complete fixing of the conformation with the coplanar arrangement of the *p*-electron density of nitrogen and the π-system of the benzene ring required for conjugation to take place:



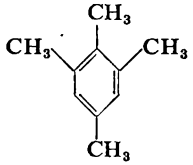

It is well known that the nitro group activates the halogen atoms in the *ortho*- or *para*-positions of the ring. This activation, however, is suppressed if the *ortho*-positions relative to the nitro group contain substituents that make the nitro group turn perpendicularly to the benzene ring. For instance, when two methyl groups are introduced into the *ortho*-positions to the nitro group in *p*-bromonitrobenzene, the rate of interaction with piperidine decreases by 25 times. *ortho*-Substituents are capable of eliminating the inactivation caused by *meta* substituents. For example, two acetyl groups can be introduced into the molecules of mesitylene VI, durene VII, and isodurene VIII by means of the Friedel-Crafts reaction, though usually only one group is introduced:




VI




VII




VIII

This is accounted for by the fact that the inactivation of the ring caused by the first acetyl group is decreased because of its coplanarity with the ring being disturbed, which occurs under the action of the *ortho*-methyl groups. The electronic effect of the four *ortho-para* substituents (the $CH_3$ groups) exerts the same influence, removing partially the inactivation caused by the *meta* substituent (the acetyl group).

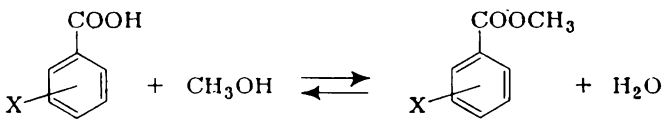
Substituents that are in the *ortho*-position to the amino or dimethylamino group make these groups turn perpendicularly with respect to the benzene ring. The break in conjugation caused in this way might be reasonably expected to increase the basicity of the amine. Simultaneously,

however, the *ortho*-substituents create steric hindrances to the formation of salts, thus lowering the basicity of the amine. On the whole, the effect of *ortho*-substituents on the basicity of aromatic amines is contradictory (18).

## 7.4. STERIC HINDRANCES IN REACTIONS OF AROMATIC COMPOUNDS

The concept of steric hindrances was first introduced into organic chemistry by Hoffmann (1872) who observed that N,N-dimethylmesitylamine is incapable of reacting with methyl iodide, i.e, does not give salts of the corresponding quaternary base. This observation served as the starting point in the works of V. Meyer (1894), whose name is associated with the original development of the idea of steric hindrances in the reactions of aromatic compounds.

It has been noted in studying the esterification of substituted benzoic acids that those acids which have substituents in the *ortho*-position to the carboxyl group are esterified more slowly and in some cases do not form esters at all. This phenomenon was later investigated by many authors. For example, Michael in 1909 published data on the rates of esterification of substituted benzoic acids by methanol.




Michael expressed his results in terms of the ratio of the rate of esterification of *ortho*-substituted benzoic acid to that of the corresponding *para*-isomer:

| | |
|---|---|
| Toluic acid | 0.54 |
| Chlorobenzoic acid | 0.68 |
| Nitrobenzoic acid | 0.44 |
| 2,4,6-Trimethylbenzoic acid | very small |

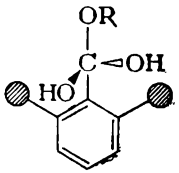
From the data given it is seen that *any ortho*-substituent lowers the rate of esterification as compared with the corresponding *para*-isomers.

Meyer had data at his disposal, indicating that the *nature* of the substit. uent plays no significant part in the manifestation of the *ortho* effect. This is also clear from the data given: *any ortho*-substituent lowers the rate of the reaction as compared with the corresponding *para*-compounds.

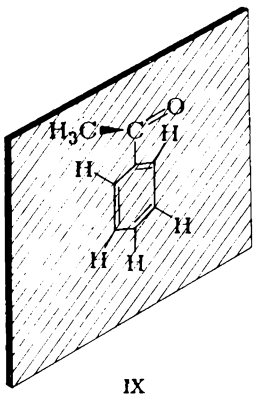
Since "negative" and "positive" substituents exert the same retarding effect, V. Meyer came to the correct conclusion that the observed effect is determined by the spatial structure of the compound, and introduced

the concept of **steric hindrances** *(steric overcrowding)*. The basic regularity established by Meyer that steric hindrances increase upon esterification with increasing size of the *ortho*-substituent remains valid at present.

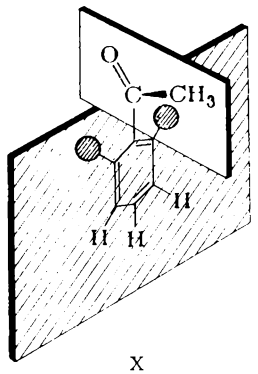
The most significant step forward after the works of Meyer was the establishment of the fact that steric hindrances manifest themselves not in all reactions. Thus, acids that are not esterified on heating with an alcoholic solution of hydrogen chloride can be converted into esters via acid chlorides, via silver salts, by the action of diazomethane, and by a number of other methods. The difficulties in the esterification reaction are, in principle, steric hindrances to the formation of a transition state in which the carbon atom of the carboxyl group must have been tetrahedral:




Steric hindrances are also manifested in reactions of *ortho*-substituted acetophenones. The carbonyl group of the unsubstituted acetophenone is entirely in the plane of the benzene ring (IX). Reagents that react with the carbonyl group can come nearer to it, approaching at right angles to the benzene ring.




IX




X

If, however, bulky substituents are in the *ortho*-positions (X), the acetyl group is perpendicular to the plane of the benzene ring and the approach

of the nucleophilic reagent to the carbonyl carbon is blocked on all the sides: from below by the benzene ring, from above by the $CH_3$ group, and from the right and left by the *ortho*-substituents. In accordance with this, 2,4,6-trimethylacetophenone, for example, is incapable of forming the products of addition to the carbonyl group.

## 7.5. OPTICALLY ACTIVE AROMATIC COMPOUNDS

### 7.5.1. BENZENE DERIVATIVES WITH A CHIRAL SIDE CHAIN

A special place among optically active aromatic compounds is occupied by benzene compounds with one or more asymmetric atoms in the side chain. Compounds of this type are encountered in nature (mandelic acid, phenylalanine, ephedrine, adrenaline, etc.) and have also been prepared synthetically. Their common specific feature is the presence of the **benzene chromophore.** In view of the importance of compounds of this kind, much attention is paid to the study of optically active compounds with benzene chromophore. The study of such compounds became possible with the development of the spectropolarimetric method which enabled obtaining data on the nature of the optical-rotatory-dispersion and circular-dichroism curves in the region of absorption of the aromatic ring.

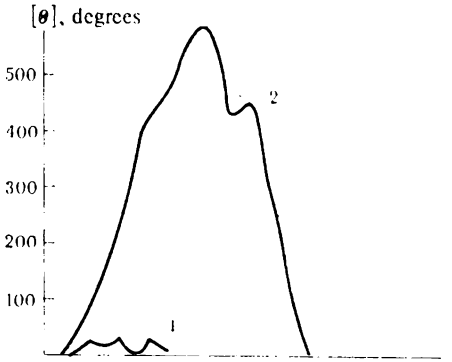
The benzene ring is characterized by three principal absorption bands in the UV spectrum: the intense 185-nm ($\varepsilon = 47{,}000$) and 205-nm ($\varepsilon = 7{,}000$) bands and the weak 260-nm band ($\varepsilon = 200$); these bands are, respectively, called the β-, *p*-, and α-bands. According to Moscowitz (19), the rotatory power $R$ of the electronic transition in the chromophore is related to the electric ($\mu_e$) and magnetic ($\mu_m$) dipole moments of the transition as follows:

$$R = \mu_e \times \mu_m \times \cos\theta$$

where θ is the angle between the directions of the electric and magnetic moments.

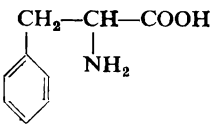
The electronic transition of the α-band has an electric moment of the transition in the plane of the ring and a magnetic moment perpendicular to this plane. At $\theta = 90°$, $\cos\theta$ is equal to zero and the rotatory power of the corresponding shift is also equal to zero. The conjugation of the aromatic ring with double bonds and with the free electron pairs on such atoms as nitrogen or oxygen disturbs the unfavourable orientation of the electric and magnetic moments, creating conditions for an increase of the rotatory power.

Figure 7.1.

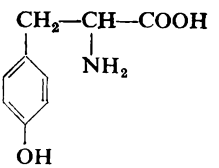



*The circular dichroism curves of phenylalanine (curve 1) and tyrosine (curve 2).*

The role of substituents with free electron pairs is clearly demonstrated by a comparison of the CD curves of two aromatic amino acids, phenylalanine and tyrosine (Fig. 7.1).




Phenylalanine

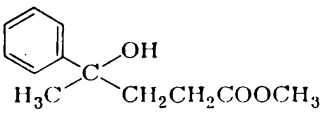



Tyrosine

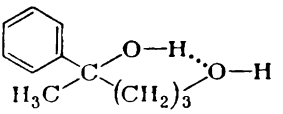
Whereas phenylalanine shows only a weak Cotton effect in the region of the long-wavelength absorption band (about 260 nm), tyrosine exhibits a strong Cotton effect in the same region. This is a consequence of the conjugation of the free electron pairs on oxygen with the π-electron system of the aromatic nucleus and of the change of the orientation of the electric and magnetic moments caused by this conjugation.

A second factor affecting the optical activity of compounds with the aromatic chromophore is a conformational factor. Conformationally mobile compounds exist as an equilibrium mixture of several conformers capable of making contributions to rotations of different signs, which cancel out on addition. Therefore, the rotation values for conformationally mobile compounds are, as a rule, not high. When the conformation is fixed, the rotation usually increases. Any particular mechanism of conformational stabilization may vary. Thus, a comparison of three compounds (20) has made it possible to assume that the appreciable

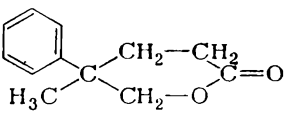
Cotton effect observed for compound XII (in contrast to compound XI which does not display a Cotton effect) is associated with the formation of a cyclic structure due to hydrogen bonding. The cyclic analogue XIII, as should be expected, shows a strong Cotton effect.



XI

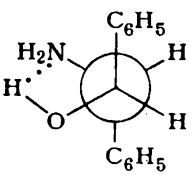


XII

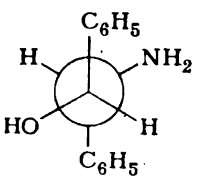


XIII

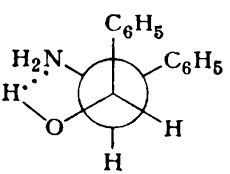
The difference between the ORD curves of diastereomeric 2-amino-1,2-diphenylethanols has been explained in an analogous way (21). The *threo*-isomer exists preferentially in a single conformation XIVa, which is favourable due to the transoid arrangement of the phenyl groups and to the formation of a hydrogen bond; this diastereomer displays a strong Cotton effect. The *erythro*-isomer exists as a mixture of several conformers: XVa, XVb, XVc; no Cotton effect is revealed on its ORD curve.



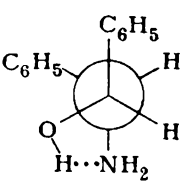
XIVa



XVa



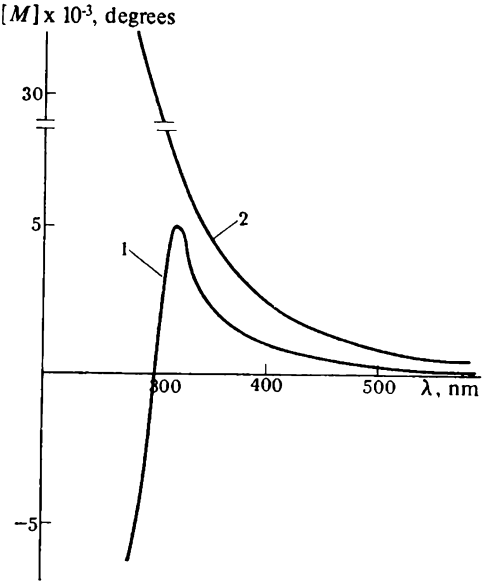
XVb



XVc

The role of conformation fixing is even more pronounced on cyclization. Thus, the UV spectra of (+)-3-methyl-3,4-dihydroisoquinoline and its non-cyclic analogue, (+)-N-benzal-α-benzylethylamine, are practically

Figure 7.2.




*The optical rotatory dispersion curves of* 3-*methyl*-3,4-*dihydroisoquinoline (curve* 1*) and N-benzal-α-benzylethylamine (curve* 2*).*

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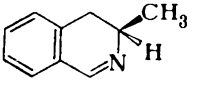
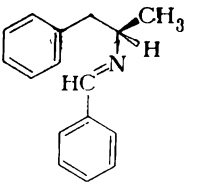
identical: this is a manifestation of the kinship of the chromophoric systems of both compounds.




The ORD curves of these compounds are however basically different: the cyclic compound shows a Cotton effect in the region of 300 nm (Fig. 7.2, curve *1*) and this is a consequence of the differences in conformation (22).

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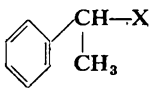
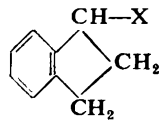
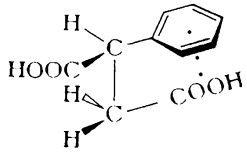
The same increase of the Cotton effect was observed by Brewster and Buta (23) on passing from α-substituted ethylbenzenes to the cyclic analogues, indanes.

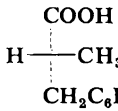


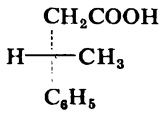

A further possible variant of conformation fixation is the *manifestation of homoconjugation*—the interaction of the mobile electrons of two chromophoric systems separated by two or more σ-bonds. Thus, phenyl-substituted amino acids and arylsuccinic acids have considerably stronger Cotton effects than the corresponding alkyl analogues. It has been suggested, as a plausible explanation, that these compounds exist in a conformation in which the benzene and carboxyl chromophores are brought closer together and that they interact with each other through space, which leads to an increased Cotton effect due to a $p$-$\pi^*$ transition in the carboxyl group (24).




The salient features of the ORD curves of α- and β-methylhydrocinnamic acids have also been accounted for by the interaction between the benzene ring and the carboxyl group (25). Acids of identical configuration have opposite signs of rotation:



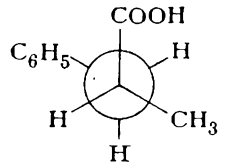

(—)-α-Methylhydrocinnamic acid
(—)-XVI

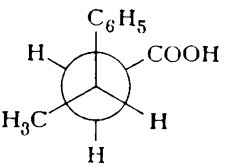



(+)-β-Methylhydrocinnamic acid
(+)-XVII

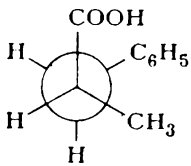
Each of these acids exists in two conformations, in which the carboxyl group and the benzene ring are in the skew position, i.e., are close

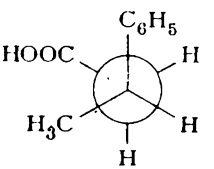
enough to each other for an interaction through space (of the homoconjugation type) to take place:

XVIa 

XVIIa

XVIb 

XVIIb

Conformers XVIb and XVIIb are less favourable since three bulky substituents are close to one another in them. The conformers XVIa and XVIIa should be regarded as the preferred ones. The homoconjugated chromophoric system HOOC—$C_\alpha$—$C_\beta$—$C_6H_5$ forms a turn of the left-handed helix in conformer (—)-XVIa and a turn of the right-handed helix in conformer (+)-XVIIa. The signs of the observed Cotton effects correspond to the signs predicted on the basis of such a consideration with account taken of the well-known spiral rule (see Chapter 4, page 298).

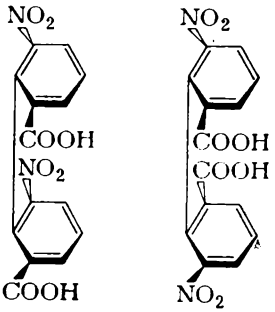
### 7.5.2. ATROPISOMERISM OF BIPHENYL DERIVATIVES

The term **atropisomerism** (meaning no rotation) covers cases of spatial isomerism due to restricted rotation about single bonds. Optical isomerism of this kind was first detected in compounds of the biphenyl (diphenyl) series*.

The history of the investigation of biphenyl isomerism provides an interesting example of how an erroneous theory may advance science for some period of time and lead to interesting discoveries. In 1907, Kaufler, basing on the results of a number of experimental investigations carried out at different times by Borodin, Kekule, and Michler, put forward the assumption that the benzene rings in biphenyl (diphenyl) compounds must be arranged one above the other. That this arrangement contradicted the normal configuration of the bonds about the carbon atom was left unnoticed. The Kaufler formula required the existence of *o,o'*-disubstituted biphenyls in two stereoisomeric forms resembling *cis-trans* isomers. It was thought at that

* The rotational isomerism of biphenyl derivatives is often called "biphenyl isomerism".—*Tr.*

time that an example of stereoisomerism of this type could be found among dinitrodiphenic acids: two acids were known, which were assigned the same structure but different configurations:

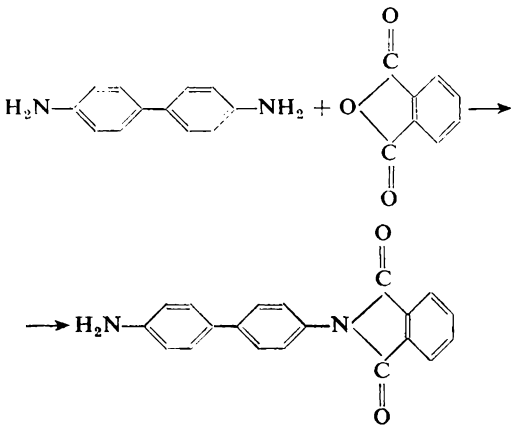



XVIII, m.p. 297°C XIX, m.p. 263°C

It was soon noticed that no element of symmetry was present in formula XIX and the conclusion was made that there must exist two optical antipodes of this acid. This prediction was soon confirmed by experiment.

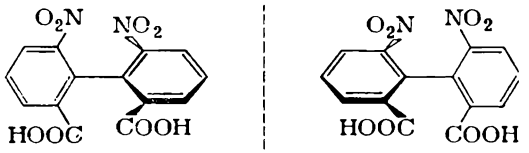
All the facts described were in excellent agreement with the Kaufler formula and served as an additional support for it. On further investigation, however, curious things were revealed. The second acid too, the one with formula XVIII, was found to be capable of existing in an optically active form. Thorough studies of its structure showed that this acid had not the structure that had been originally assigned to it: one of the nitro groups in it is in the *para*-position. Thus, the difference in melting temperature between the two acids is the result of the ordinary structural isomerism and not of stereoisomerism.

The older data on the formation of "cyclic products" in various reactions of benzidine were also checked up: a free primary amino group was detected in the product of the reaction of benzidine with phthalic anhydride; that benzidine has no dipole moment also contradicted the Kaufler formula. On this basis, the Kaufler formula was rejected, and benzidine was assigned a linear structure and the product of its reaction with phthalic anhydride, the formula with a free amino group:



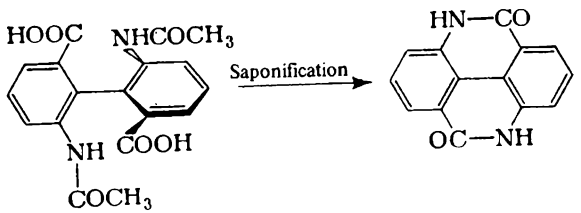
But how do optically active dinitrodiphenic acids appear then? The linear formula does not allow for their existence. The answer to this question was given in the 1920's by Kenner and Christie (1922) and Meisenheimer (1927).

The optical activity of dinitrodiphenic acid and similar compounds is accounted for by the fact that the substituents in the *ortho*-positions prevent the free rotation of the phenyl rings about the single bond that links them. As a result of this, two mirror-image forms appear:




The optically active compounds of the biphenyl series are rotational isomers (conformers) that have become stable due to the peculiar steric conditions in their molecules. We have already said (see page 33) that in such cases it is difficult to draw a clear-cut boundary line between stereoisomerism and conformation.

To create structural asymmetry, the phenyl rings must not lie in the same plane. The fact that optical activity disappears with the planar arrangement of the rings was confirmed by the following conversion:

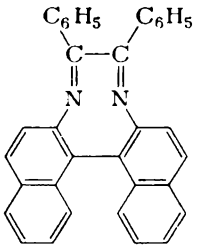



An optically active compound

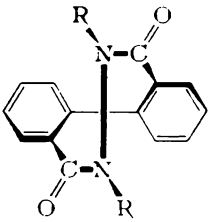
An optically inactive compound

Optical activity disappears here as a result of the phenyl rings being fixed in one plane during the formation of lactam rings. One should not, however, think that this type of cyclization is invariably accompanied by the disappearance of optical activity. If a many-membered non-planar ring is formed, optical activity is retained. This has been

observed, for example, for compound XX. The conformation of such compounds has been studied on cyclic hydrazides of the type XXI (26).

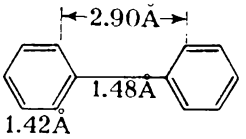


XX

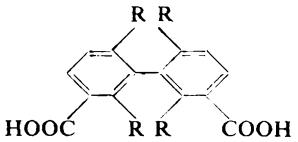


XXI

For the free rotation to be hindered, the substituents must "cog-wheel" with one another and this is possible only when they have definite sizes. These sizes can be calculated on the basis of the biphenyl model:



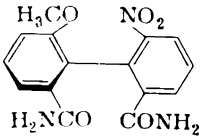

It is obvious that the ability to exist in non-planar optically active forms must be displayed only by those biphenyl derivatives in which the sum of the van der Waals radii of the *ortho*-substituents is not less than 2.90 Å. The correctness of such a model conception has been confirmed for compounds of the type




If R is a fluorine atom (radius 1.39Å), then the sum will be smaller than that required for overlapping, and such a compound must not be resolvable into optical antipodes; experiment has confirmed this conclusion. The sizes of the $OCH_3$ group (radius 1.45 Å) prove to be sufficient for overlapping. Experiment shows that the corresponding compound can be prepared in an optically active form

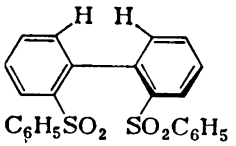
but is readily racemized (at —17°C the half-racemization period is 2.5 min). If R is a chlorine atom (radius 1.69 Å), the overlapping becomes significant: the corresponding compound can be prepared in an optically active form and is not racemized under ordinary conditions.

Not in all cases, however, can the optical stability of diphenic compounds be explained in such a simple way on the basis of geometric considerations. As an example may be cited compounds that differ by the nature of substituents in the "non-blocking" (*meta*-) position. The compound has been used for a detailed study of the dependence of

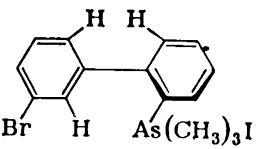



racemization on the nature of the solvent (27). An attempt was also made (28) to directly relate the rate of racemization to the viscosity of the solvent but no correlation was revealed.

Optically active compounds of the biphenyl series must not necessarily contain four or three substituents in the *ortho*-positions, as is the case with the examples considered above. Cases are known when two or even one substituent is enough for the manifestation of atropisomerism — in these cases the substituent must be so large that even the hydrogen in the *ortho*-position of the neighbouring ring would not make possible the rotation:




$[\alpha]_{579} = -24.6°$




$[\alpha]_D = +1°$

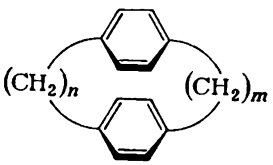
All atropisomers with one or two substituents in the *ortho*-position are rapidly racemized even when allowed to stand. This serves as one of the proofs that optical activity is not caused by an impurity of the optically active reagent used for resolution.

There are some steric hindrances to the coplanar arrangement of biphenyl rings even in the unsubstituted biphenyl; this follows from the fact that, according to the data of electron diffraction measurements

in the gas phase, the benzene rings of biphenyl are at an angle of about 45° to each other (29). But in the absence of "blocking" *ortho*-substituents the potential energy barrier to rotation about the bond joining the rings is not high and spatial isomerism is replaced by conformational phenomena. This is one of the most spectacular examples of the absence of a sharp boundary line between spatial isomerism and conformation.

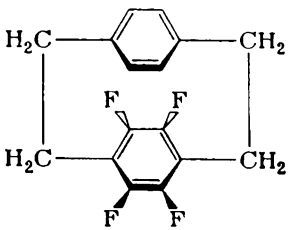
### 7.5.3. CYCLOPHANES AND ANSA COMPOUNDS

Very interesting compounds are known to exist, which exhibit atropisomerism; these are so-called **paracyclophanes** (for a review of this class of compounds, see ref. 30) having the structure




The benzene rings in paracyclophanes with small *n* and *m* are arranged one above the other just as the shelves in a bookcase. Their π-electron systems are brought close together and are, to a certain extent, united into a single electronic system. This manifests itself, for example, in that the acetyl group introduced into one of the rings retards the acetylation of the other ring.

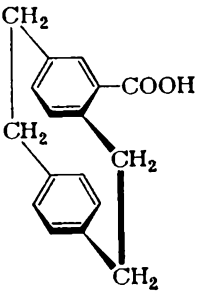
The interaction of the two benzene rings of paracyclophanes is also shown by the UV spectra. In the compound




the transannular interaction reveals itself in the form of a band in the UV spectrum at 297 nm. This band arises as a result of an electronic transition of the donor-acceptor type (31). A similar band (in the form of a shoulder at 302 nm) is also present in the unsubstituted paracyclophane; hence, it shows a weak π-π transannular interaction too.

The hindrances to the free rotation of benzene rings are also present in paracyclophanes with $m = 3$ and $n = 4$. But if the benzene rings are linked by chains consisting of four or more $CH_2$ groups, the rotation becomes possible.

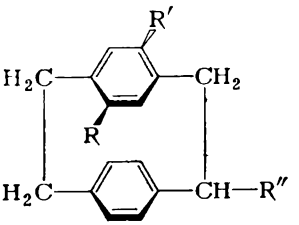
In unsymmetrically substituted rigid paracyclophanes, the presence of even one substituent in one of the benzene rings is enough for the structure to become chiral. This has been proved by the preparation of paracyclophanecarboxylic acid and other analogous compounds in an optically active form (32). The configurations have also been elucidated: for example, the (+)-antipode of paracyclophanecarboxylic acid has formula **XXII** (33). All these compounds are regarded as structures with a plane of chirality.




XXII

The amide of this acid was converted, by means of the Hoffmann rearrangement, into the corresponding amine, whose amino group was replaced, by way of diazo reactions, with chlorine and hydroxyl. The optical activity was retained in all these conversions.

Another series of optically active paracyclophanes (34) have the following general formula:




$R' = CH_3$; $R = R'' = H$

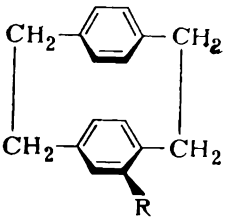
$R' = R = CH_3$; $R'' = H$

$R' = R = H$; $R'' = COOCH_3$

$R' = R = H$; $R'' = CH_2OH$

A simpler related compound, whose optical activity is caused by the chirality of the paracyclophane structure and the asymmetric centre in the side chain (XXIII, $R = CH_2—CHOH—CH_3$), has been proved

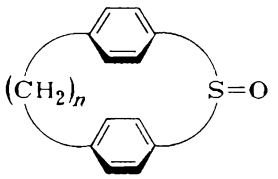
to have absolute configuration XXIII by means of chemical correlation and NMR data (35).



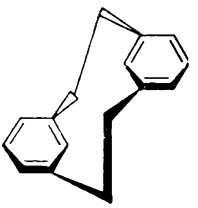
XXIII

The antipode of the given configuration has a (+)-rotation (independently of the configuration of the asymmetric centre in the side chain, which introduces a much lesser contribution to the total rotation).

Bridges can be formed not only by carbon atoms: compounds with sulphur-containing bridges may be exemplified by substances of the general formula XXIV. These compounds have been utilized to study the dependence of the rotational barriers of benzene rings on the length of the bridge (36). The values of $\Delta G^{\neq}$ at $n = 4$, 5, 6, and 7 are, respectively, 105, 98, 58, and 38 kJ/mole.

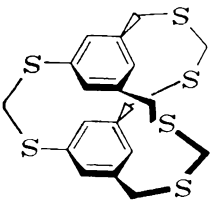


XXIV



XXV

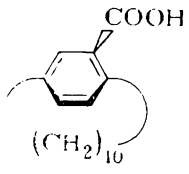
Compounds are also known, in which the benzene rings are joined by bridges situated in the *meta*-position—**metacyclophanes** XXV (37). With the plane as a chiral element, substituted metacyclophanes may exist in optically active forms (38). Of interest is a cyclophane with *three* bridges in the *meta*-positions, XXVI:

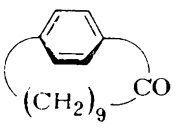


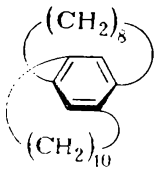
XXVI

Inside such a "cage" is an empty space which may accommodate small molecules of other substances as guests (39).

The paracyclophanes also include compounds which contain only *one* aromatic ring with an aliphatic bridge fixed in the *para*-position; for example, (40):

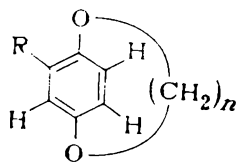



If there are substituents in the benzene ring or in the bridge, such compounds are chiral; many of them can be prepared in an optically active form.

The restricted rotation of the benzene ring is also responsible for the chirality of other compounds, XXVII, which are called **ansa compounds.**

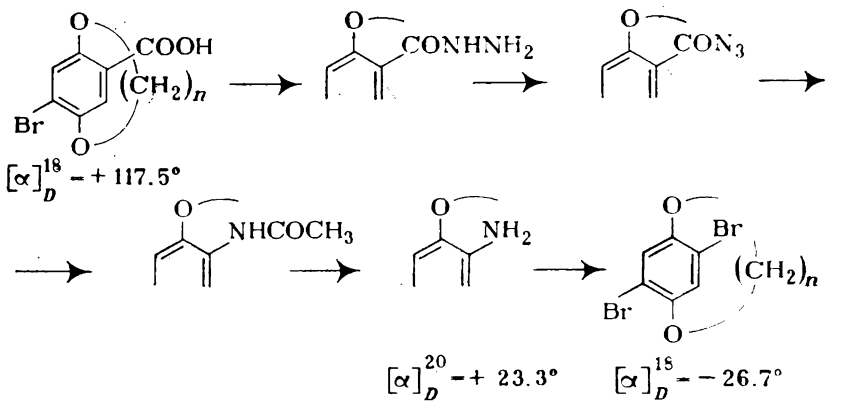



XXVII

The number of methylene groups in the polymethylene ring of such compounds may vary. With a certain minimum size of the ring the free rotation of the hydroquinone ring is stopped; two antipodes appear for such compounds. It has been established that at $n = 10$ the racemization proceeds with an immeasurably faster rate even at 0°C; with $n = 9$ there can be obtained an optically active compound with a half-racemization period of 1835 min at 82.5°C; with $n = 8$ no racemization takes place even at 200°C. If the corresponding spatial models are built with account taken of the sizes of atoms and interatomic distances, it will be seen that with $n = 9$ even the unsubstituted side (strictly

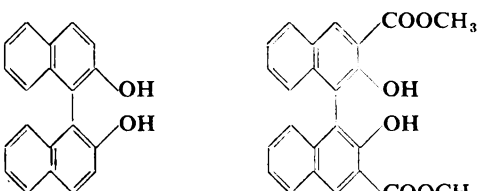
speaking, the one that bears only hydrogen atoms) of the benzene ring cannot rotate through such a polymethylene ring.

A series of conversions have been accomplished with the optically active ansa compound obtained and it has been shown that the optical activity is retained (only fragments of the molecules are shown at the intermediate stages):




### 7.5.4. OTHER TYPES OF ATROPISOMERISM

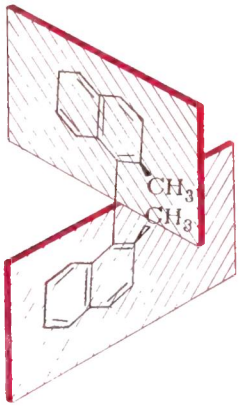
Like biphenyl derivatives, the correspondingly substituted dinaphthyls are also capable of exhibiting atropisomerism (41); for example:

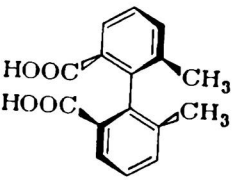



XXVIII

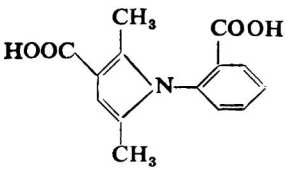
The configurations of a number of derivatives of dinaphthyl and biphenyl have been determined on the basis of compound XXVIII

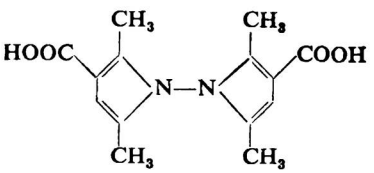
by means of chemical correlation (42). The configurations of the (—)-antipodes are represented by the following formulas:



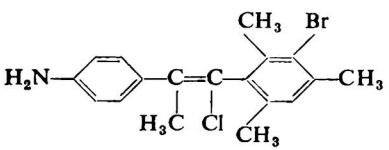




A system with restricted rotation can be built also with the participation of heterocyclic rings; for example:

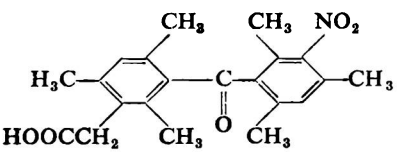


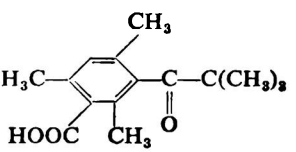




There has also been studied a series of optically active atropisomers in which one phenyl ring is linked to an arylsubstituted ethylene (43):



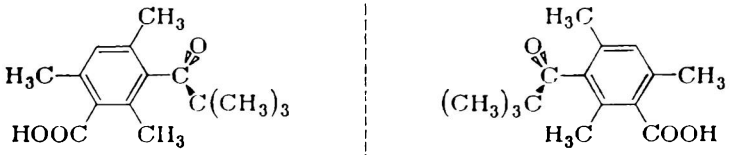

Optically active atropisomeric compounds of the following type have been described in the literature (44):




XXIX

It may seem that in compound XXIX the *tert*-butyl group as a symmetrical substituent cannot create molecular asymmetry. But, as a matter of fact, there exist two atropisomeric mirror-image forms, the spatial structures of which are as follows:



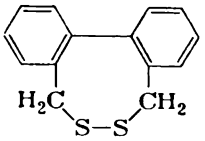

Thus, the role of the second unsymmetric substituent is played by the entire grouping $(CH_3)_3C—CO—$ swung out of the plane of the aromatic ring by the *ortho*-substituents.

In 1967, there was published a work the title of which sounded paradoxically and was at first thought to be a misprint: "Optical Activity of Symmetrically (?!) Substituted Acetic Acids". Acquaintance with this work shows that the author is dealing with a case of atropisomerism in the diphenylmethane series. The optically active compounds obtained have the following structure (45):

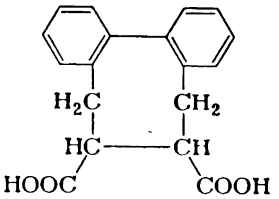
Both aromatic rings are arranged in two mutually perpendicular planes, just as in biphenyl. In order to create steric hindrances to the rotation about the bonds to the central carbon atom, the *ortho*-substituents R must be sufficiently large (an isopropyl or *tert*-butyl group). The activation energy of the racemization of these compounds is of the order of 80 kJ/mole and the half-racemization period at 25°C is 100 min.

## 7.6. CHIRAL BENZOCYCLOALKANES

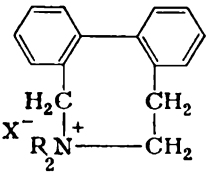
Non-planar cycloalkane rings, the conformation of which is "frozen" by the fused-to benzene rings, are responsible for the optical activity of a number of compounds. One of the simplest substances of this type is a biphenyl derivative of structure XXX.



XXX

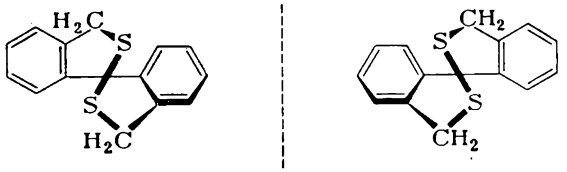


XXXI



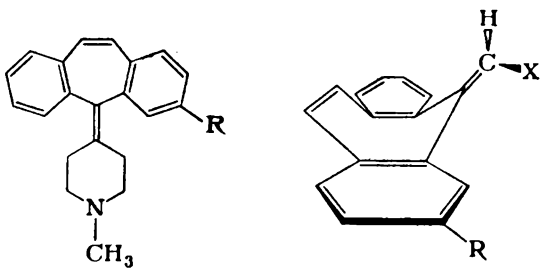
XXXII

Compound XXX was obtained in an optically active form; it proved rather stable (the activation energy of racemization is 115 ± 2 kJ/mole), in contrast to its analogues XXXI and XXXII which are rapidly racemized. According to Luttringhaus and Rosenbaum (46), the central sulphur-containing eight-membered ring of compound XXX exists in asymmetric non-planar "pseudo-chair" and "pseudo-boat" forms. The antipodes may be represented thus:



The answer given by these authors to the question as to why compound XXX has an enhanced optical stability is not quite definite (the answer is that the longer C—S and S—S bonds create conditions for the formation of more stable asymmetric conformers).

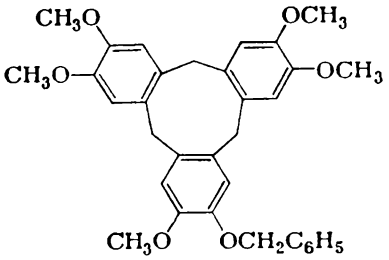
The cycloheptane ring, the rigidity of which is increased by the double bonds and the fused-to benzene rings is also capable of creating molecular-asymmetric structures, say, compound XXXIII (47). Compound XXXIII and related compounds have a spatial structure in which the central seven-membered ring is rigidly fixed in the boat form, as, for example, in XXXIV.



XXXIII XXXIV

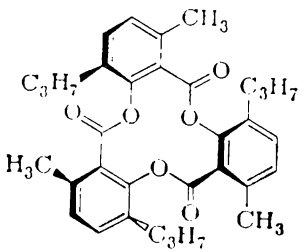
The cyclic structure in compounds of this type is symmetrical. Molecular asymmetry can be created in two ways: due either to the non-identity of the "benzene wings" (as in structure XXXIII) or to the non-identical substituents of the seven-membered ring (as in structure XXXIV).

The asymmetry in a compound with a nine-membered central ring is of the same nature (48):




## 7.7. OPTICAL ACTIVITY OF TRI-*o*-THYMOTIDE

A peculiar case of asymmetry was described by Newman and Powell (49) who succeeded in preparing tri-*o*-thymotide in an optically active form; it has the following structure:



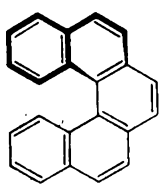

Molecular asymmetry develops here as a result of the phenyl rings not lying in the same plane. They are in an inclined position relative to one another, forming a structure resembling a right- or left-handed three-bladed propeller. The compound rapidly undergoes spontaneous racemization.

## 7.8. HELICENES AND HELICAL PHENANTHRENES

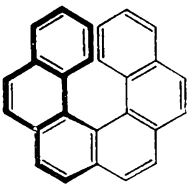
Helicenes are compounds in which several aromatic rings joined by *ortho*-junction form structures of the helical type. Since the helix has

no elements of symmetry and may be left- or right-handed in orientation, conditions are created for appearance of optically active compounds.

Stereoisomerism of this type is encountered in helicenes with a minimum number of benzene rings equal to five:



(+)-Pentahelicene



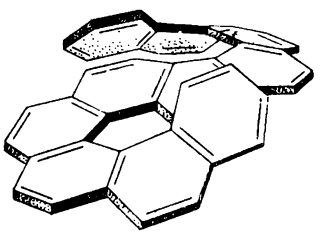
Hexahelicene

Helicenes are known, which have a larger number of benzene rings: hepta-, octa-, and nonahelicenes, and helicenes with side chains (50).

Apart from other methods, absolute photochemical asymmetric synthesis can also be used to prepare optically active helicenes (51). Although the optical purity in these syntheses is only fractions of a per cent, the rotation of the compounds obtained amounts to 20-30° since optically active helicenes have $[\alpha]_D$ of up to 7000°.

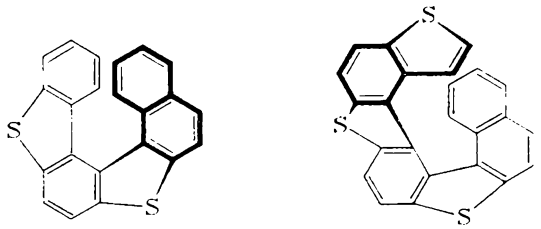
Helicenes are readily racemized: this occurs on heating them above their melting point; $\Delta G^{\neq}$ is 155 kJ/mole for hexahelicene and 102 kJ/mole for pentahelicene.

An example of a twin helicene is known (**XXXV**), which is capable of existing in *meso*- and racemic forms (m.p. 400-402°C and 390°C, respectively, (53); the spatial structure of the optically active form of this compound is shown below:



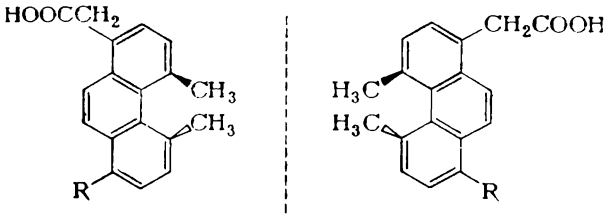
XXXV

The heterocyclic analogues of hexahelicene have also been prepared in an optically active form (54):



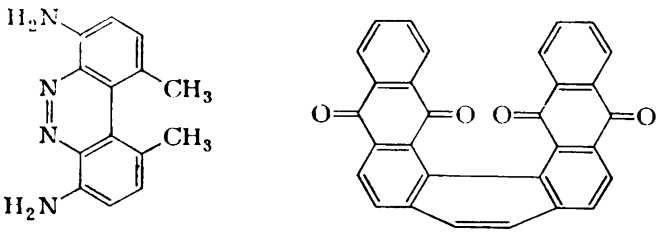
XXXVI

The absolute configuration of compound **XXXVI** has been determined; the (+)-antipode has the shape of a right-handed helix (55). The helical shape similar to that of helicenes can also be built in phenanthrene derivatives that have substituents in positions 4 and 5. The substituents can be arranged here only by distorting the phenanthrene ring. The system becomes then chiral and, hence, can be resolved into antipodes. The validity of this conclusion was proved by Newman and coworkers (56) on compounds of the type **XXXVII**, the mirror-image forms of which may be represented as follows:



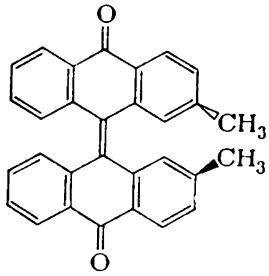
XXXVIIa XXXVIIb

Another example (57) is optically active compound **XXXVIII**, for which $[\alpha]_D$ is about 50° (in methanol). When this compound is heated up to 60°C for 1 hour, complete racemization takes place. The phenanthrene derivative XXXIX has also been prepared in an optically active form.



XXXVIII XXXIX

Optically active helianthrones belong to the same type of compounds. An example is compound XL (58):

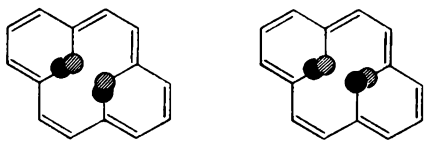


XL

The specificity of many of the compounds considered in Sections 7.6 and 7.8 consists in that their structural formulas are *symmetric* (for example, XXX, XXXI, XXXVIII); chirality is produced due only to the spatial form.

## 7.9. ANNULENES

Annulenes are macrocyclic compounds with a system of conjugated double bonds. The annulenes display specific stereochemical characteristics of their own. Thus, for example, [14]annulene when subjected to chromatographic analysis on silica gel coated with silver nitrate is separated into two rapidly interconvertible isomers, which differ in the mode of overlapping of intraannular hydrogen atoms (59):

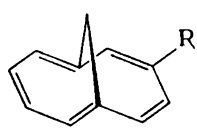


$\lambda_{max}$ = 317; 378 nm $\quad$ $\lambda_{max}$ = 317; 380 nm

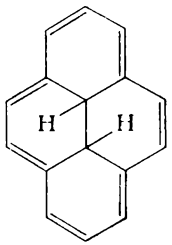
$\delta$ = 5.58 ppm $\quad$ $\delta$ = 6.07ppm

In this case, we are, in principle, dealing with "frozen" *conformers.*

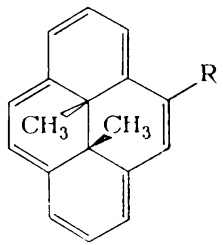
Optically active annulenes are also known to exist (60); examples are the derivatives of 1,6-methylene[10]annulene:



A peculiar "annulene" structure of the polycyclic type is possessed by dihydropyrene XLI:




XLI




XLII (R=$CH_3$, COOH)

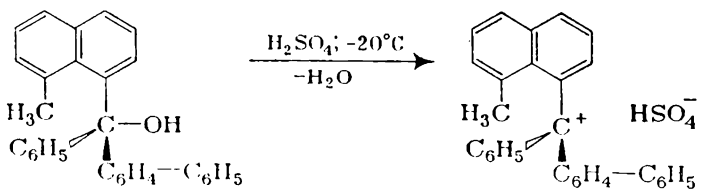
When two substituents are added to the central carbon atoms of dihydropyrene and one substituent to the peripheral atom, the molecule becomes chiral. The corresponding compounds have been obtained in optically active forms. An example is compound XLII (61).

## 7.10. COMPOUNDS OF THE TRIPHENYLMETHANE SERIES

Murr and coworkers have described optically active compounds of the triphenylmethane series with the asymmetry of the central carbon atom. One example is phenyldiphenylyl-(α-naphthyl)-carbinol (62):

$$\alpha\text{-}C_{10}H_7\text{—}C(C_6H_4\text{—}C_6H_5)(C_6H_5)\text{—OH}$$

A compound of this type enabled the optical activity of an asymmetric carbonium ion to be observed for the first time:




XLIII, $[\alpha]_D = +76°$ XLIV, $[\alpha]_D = +1940°$

The ion XLIV is formed by the short-time action of concentrated sulphuric acid in the cold. If the reaction mixture is diluted with water after several minutes, the carbinol XLIII will be re-formed but it will however have the left-handed rotation: in the reaction (+)-XLIII → (+)-XLIV → (—)-XLIII there is observed a Walden inversion (63).

It is known that carbonium ions have a planar structure (see Chapter 4, page 268), and therefore racemization occurs during the conversion of the asymmetric atom into a carbonium-ion centre. Retention of optical activity in the conversions considered above is an exceptional case, this being possible because the triphenylmethyl cations may have helical chirality (64), like trithymotide (see page 506).

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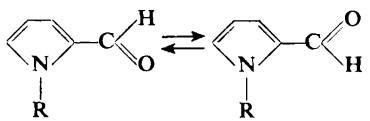
CHAPTER 8

# Stereochemistry of Heterocyclic Compounds

## 8.1. AROMATIC HETEROCYCLES

Aromatic heterocyclic compounds—pyridine, pyrrole, thiophen, furan and others—are analogous in their geometric structure to benzene rings: they are planar systems, which in the presence of side chains or when incorporated into complex polycyclic structures may display the same configurational and conformational features as aromatic compounds.

Thus, for example, substituents that are linked to heterocyclic rings may be in various conformations. As an example, we shall give the results of a study of the conformations of N-alkylated 2-formylpyrroles. The most favourable here are two conformations in which the ring and the C=O bond lie in the same plane and are conjugated:

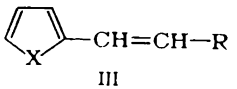


I II

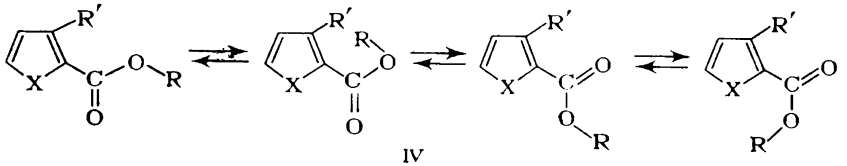
It has been shown, by means of NMR spectroscopy, that with any R the conformation I is more preferred (1). Analogous results have been obtained in the investigation of aldehydes of the furan and thiophen series (2), although the conclusions made by some of the authors as

to the stability of individual conformations on the basis of IR spectra were somewhat different.

The side-chain conformations have been studied for other derivatives of furan and thiophen as well — thienyl- and furylethylenes III (3), furan- and thiophencarboxylic acids IV (4).

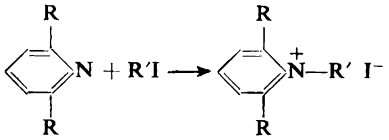


III



IV

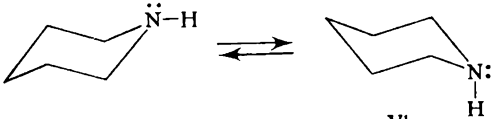
It has been found in the case of the conversion of 2,6-dialkylpyridines into pyridinium salts (the Menshutkin reaction), that the increase of pressure partly removes the steric hindrances (5):



## 8.2. THE SHAPE OF SIX-MEMBERED SATURATED HETEROCYCLES

The stereochemistry of saturated six-membered heterocycles has many features in common with the stereochemistry of cyclohexane. Like cyclohexane, the six-membered heterocyclic rings of piperidine and tetrahydropyran exist predominantly in the chair form. The boat form is less favourable, its energy being higher by 20 (for piperidine) and 16 (for tetrahydropyran) kJ/mole.

The assignment of the chair form does not yet solve the problem of the conformation of the piperidine ring; the question that remains to be answered is whether the hydrogen (form Va) or the free electron pair (form Vb) occupies the equatorial position at the nitrogen atom:



Va Vb

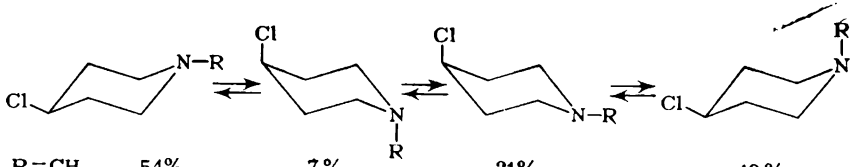
The data available in the literature as to which of the conformations is the preferred one are contradictory. The conclusion made on the basis of measurements of the Kerr constants is that the preferred conformation is the form Vb with an axially oriented hydrogen. From the dipole moments and IR spectra, however, it was deduced that the form Va with an equatorial hydrogen atom is more preferable. The NMR data that indicate the axial orientation of the hydrogen of the NH group should be regarded as the most reliable (6).

More unanimous are the estimations of the conformations of N-alkylpiperidines: all the data indicate that the alkyl group occupies the equatorial conformation. This conclusion has been made, in particular, in the investigation of the dipole moments. The same result was obtained by the study of the reactions of gaseous N-methylpiperidine with deuterated acids (e.g., $D_2SO_4$); the formation of a salt under these conditions proceeds more rapidly than is the conformation changed.

The conformation of N-chloropiperidine has been studied by the spectroscopic method (7). In the liquid state at 0°C, 94 per cent of this compound is in a conformation with the chlorine atom in the equatorial position and 6 per cent with the chlorine atom in the axial conformation. The enthalpy difference between the two conformers is $6.2 \pm 1$ kJ/mole. On freezing the molecules pass entirely into the equaorial conformation.

## 8.3. CONFORMATIONS AND CONFIGURATIONS OF COMPOUNDS OF THE PIPERIDINE SERIES

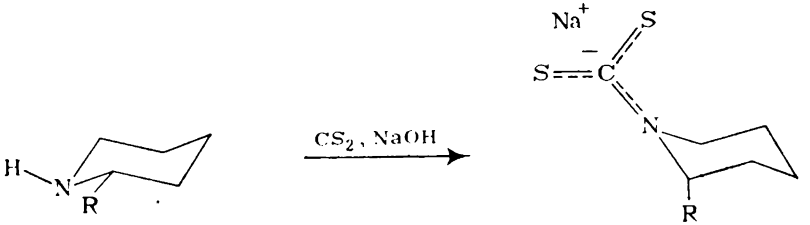
The rules concerning the orientation of substituents in the piperidine ring correspond, in general, to the regularities existing in the cyclohexane series: usually (especially, if we are speaking of the alkyl side chains) the equatorial position of the substituent is more favourable. Thus, the following contributions of the individual conformations have been found by NMR spectroscopy (8) for 4-chloro-N-alkylpiperidines:




| | | | | |
|---|---|---|---|---|
| $R=CH_3$ | 54% | 7% | 21% | 18% |
| $R=C(CH_3)_3$ | 70% | 0% | 30% | 0% |

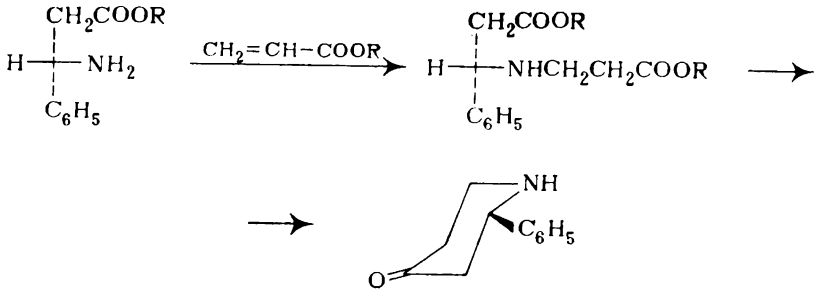
The existence of *four* conformations may be expected in a general case, but with large R the axial orientation of these substituents becomes highly unfavourable.

Forrest and Ray (9) noted that when the conformations of alkylpiperidines are to be determined by NMR spectroscopy, use should not be made of carbon disulphide as the solvent since the dithiocarbamate derivatives formed in the solution may have a conformation different from that of alkylpiperidines themselves:



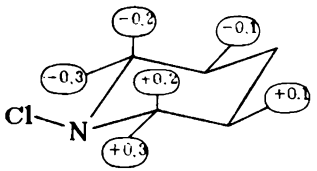

Just as in the case of the cyclohexane series, the study of optically active derivatives by spectropolarimetric methods plays an important part in the investigation of the spatial structure of compounds of the piperidine series. Thus, the study (10) of (—)-2,2-dimethyl-6-phenyl-4-piperidone has shown that there is a trough on the ORD curve of this compound in the region of 310-320 nm, which is retained also for the hydrochloride and acetate of that compound. When a drop of concentrated HCl is added to the methanol solution of the compound, the Cotton effect disappears (as a result of the formation of a hemiacetal). All this is evidence that the Cotton effect is due to the optical activity of the carbonyl absorption band, just as in the corresponding cyclohexanones (see page 395).

This close relationship allows one to raise the question: Could the octant rule, which is valid in the cyclohexanone series, be extended to compounds of the piperidine series? The answer to this question could be given by studying the optical rotatory dispersion of piperidones of known absolute configuration. For this purpose, use was made of the synthesis of 2-phenyl-4-piperidone from an optically active compound of known configuration:

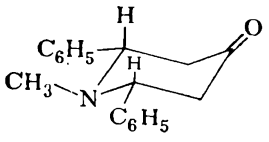


The configuration of the piperidone formed follows from the configuration of the starting compound, and the conformation is determined by the necessity of the equatorial orientation of the phenyl group. The resulting piperidone turned out to be levorotatory, which corresponds to the position of the substituent in the far upper right octant.

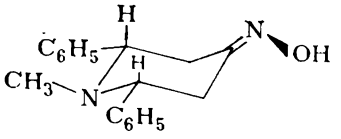
The regularities of optical rotation have been studied for other derivatives of piperidine as well (11). Thus, based on the study of the optical rotatory dispersion and circular dichroism of a number of compounds, Ripperger and Pracejus (12) drew up a diagram showing the contributions of the $CH_3$ groups occupying different structural and spatial positions to the Cotton effect of optically active N-chloropiperidines (enclosed in circles are the values of the dichroic absorption coefficient, $\Delta\varepsilon$, at 270 nm).




The optical activity of the oxime of *cis*-2,6-biphenyl-N-methyl-4-piperidone is caused by some peculiar factors. The starting piperidone VI has a plane of symmetry passing through the nitrogen atom and the carbonyl group: it cannot therefore be optically active. In its oxime, VII, the hydroxyl group, which does not lie in the indicated plane, renders the entire structure asymmetric and creates conditions for the appearance of optically active forms (13).

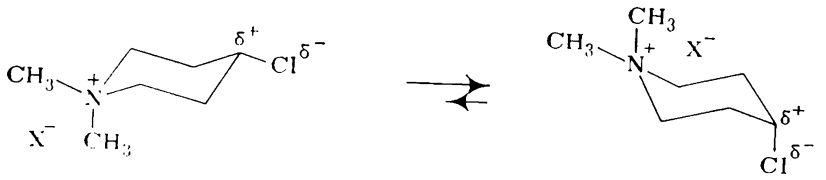



VI

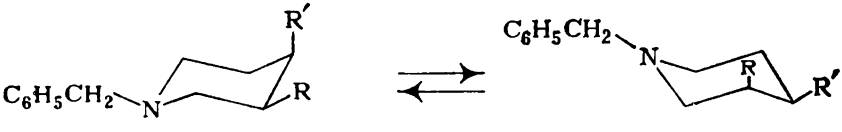



VII

The conformations of 4-piperidones have also been studied by NMR spectroscopy. For example, it has been shown (14) that in N,N-dimethylpiperidinium salts, the more favourable conformation for the hydroxyl group or the chlorine atom in position 4 is the axial conformation (the right-hand one of those shown below), which is stabilized by the transannular electrostatic interaction:

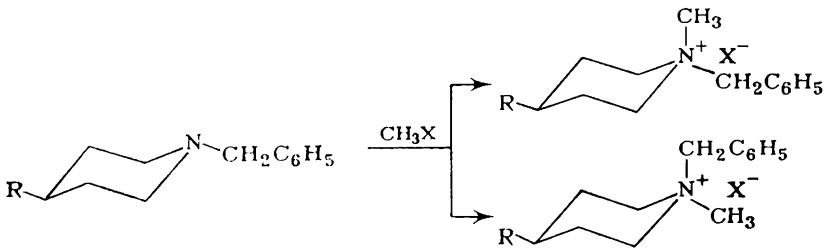


The conformation of N-benzyl-3,4-dialkylpiperidines has been elucidated by taking advantage of the fact that the magnetic non-equivalency of diastereotopic benzyl protons reveals itself in the NMR spectra only if the substituent in position 3 is axial (15), i.e., the compound is in the conformation given below (VIIIb):

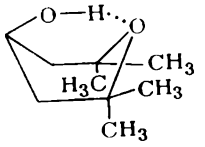


VIIIa VIIIb

The equatorial orientation of the substituent at the nitrogen atom is more favourable, but on conversion of N-substituted piperidines into quaternary piperidinium salts there arise *both* possible configurations at the nitrogen atom, as illustrated, for example, by the following data (16):



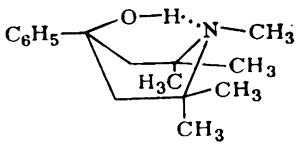
In certain special cases, the boat form too has been shown to exist for six-membered heterocyclic compounds (17); an example is compound IX:



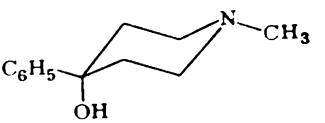
IX

The boat form in this compound is fixed by hydrogen bonding (its existence is confirmed by the IR spectra). The significant role of the hydrogen bond follows from the fact that no boat form has been found in the corresponding thio analogue (the energy of the hydrogen bond S···H is lower than that of the O···H bond).

The boat form is also possessed by the structurally related piperidine derivative X (its IR spectrum also shows a strong intramolecular hydrogen bond), whereas compound XI, which has no *gem*-dimethyl groupings, exists in the chair form (the IR spectrum reveals the presence of a free OH group):



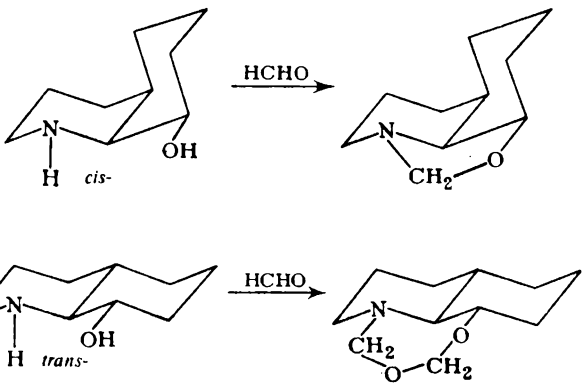

X



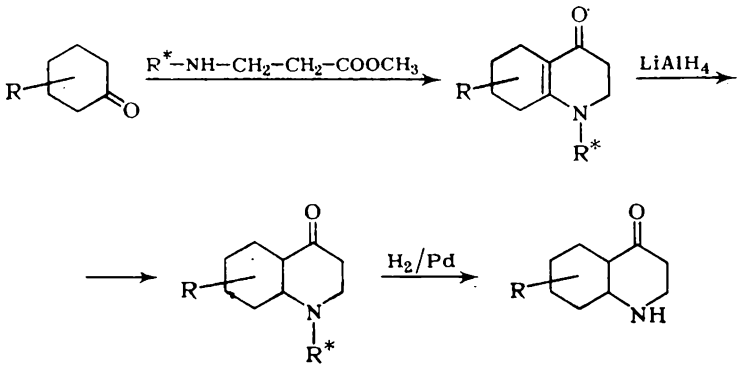

XI

## 8.4. BICYCLIC NITROGEN-CONTAINING HETEROCYCLES

Decahydroquinoline exists in two stereoisomeric forms with the *cis*- and *trans*-junction of the rings, like decalins (see page 379). The existence of *cis-trans*-isomeric decahydroquinolines was first proved by Hückel in 1927. The isomers differ not only in physical but also chemical properties, as can be seen in the reaction of 8-hydroxydecahydroquinolines with formaldehyde:

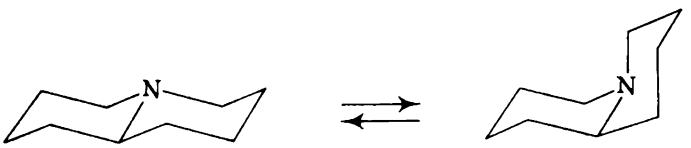


An interesting route to optically active compounds of the decahydroquinoline series has been proposed by Potapov and coworkers (18):

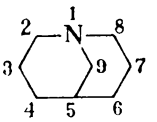



Using various alkylcyclohexanones as the starting compounds and the product of the condensation of methyl acrylate with optically active α-phenylethylamine [R* = $CH(CH_3)C_6H_5$], one can obtain various 4-decahydroquinolones and their reduction products.

*cis*- and *trans*-Decahydroquinolines are stable stereoisomeric forms existing separately. In contrast to this, the analogous forms of a related cyclic structure, **quinolisidine** (see the review article by Riddell, ref. 19), are readily interconvertible. In this case, the *cis-trans* forms are only conformers that cannot be isolated in the individual state:



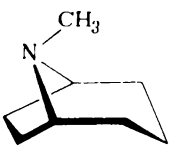

Another structure with a common nitrogen atom is 1-azabicyclo-[3.3.1]nonane XII, whose derivatives have been studied by Hughes and Hudec (20).



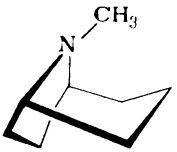

XII

The bicyclic system of the nitrogen-containing heterocyclic compound tropane constitutes the parent ring system of a large group of naturally

occurring compounds — tropane alkaloids. The tropane ring can exist in two conformations. In one of them (XIIIa) the piperidine ring has the chair form and in the other (XIIIb), the boat form:

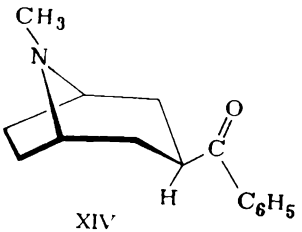


XIIIa

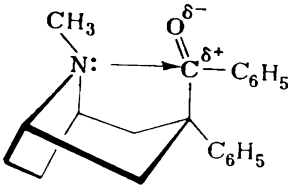


XIIIb

The data available in the literature show that, depending on the nature of the substituents, either of the two conformations may prove more favourable. As an example, we may compare two compounds, 3-benzoyltropane XIV and 3-phenyl-3-benzoyltropane XV. The first of these compounds has UV and IR spectra with ordinary bands of the carbonyl group. No carbonyl bands have been detected in the spectra of the second compound; this is believed to be a consequence of the flipping of the piperidine ring into the boat form and of the transannular interaction of the nitrogen atom with the carbonyl group (32):

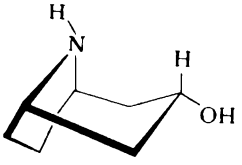


XIV

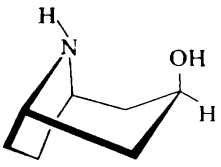


XV

The facile migration of the acyl groups from nitrogen to oxygen and vice versa in compounds of the nortropine series is also explained by the possibility of the ready conversion of the piperidine ring of tropane into the boat form. Nortropine exists in two stereoisomeric forms which differ in the orientation of the hydroxyl group: it is equatorial in nortropine and axial in norpseudotropine:

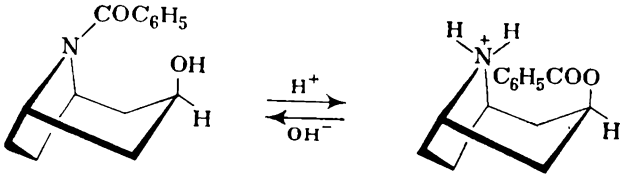


Nortropine



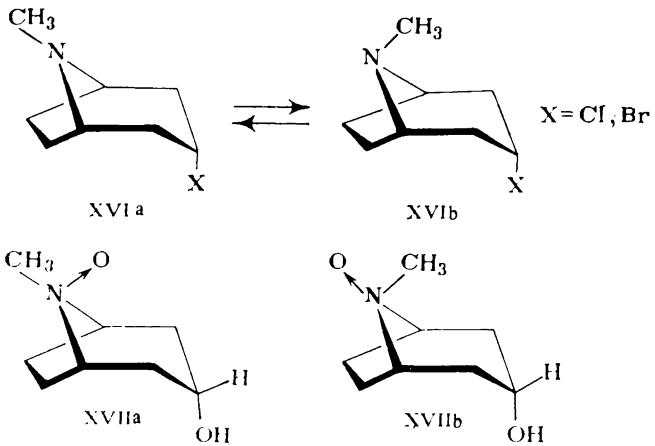
Norpseudotropine

In the benzoyl derivative of norpseudotropine, the acyl group can easily migrate from nitrogen to oxygen and vice versa. Such an intramolecular migration is possible only in the boat form:




The benzoyl group of the corresponding derivatives of nortropine is incapable of migration since the nitrogen and oxygen in this stereoisomeric form are far apart from each other.

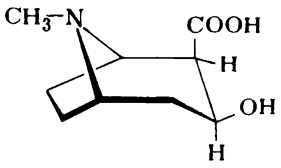
3α-Halotropanes XVI and tropine N-oxide XVII exist in conformation with the piperidine ring in the chair form. Two forms can exist due to the different spatial orientation of the substituents at the nitrogen atom. In halotropanes, these are *conformers* XVIa and XVIb which exist in equilibrium in the ratio of 9 : 1, respectively (21):



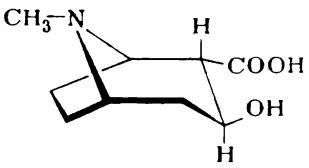

In the case of the tropine N-oxide, both forms are stable *stereoisomers* which can be separated, for example, by crystallization from a mixture of alcohol and ether (22).

Tropane and tropine have a plane of symmetry and cannot therefore exist in optically active forms. When substituents are introduced at positions 2, 4, 6 or 7, the symmetry is disturbed and optically active forms become possible for the corresponding compounds. Asymmetry is acquired here not only by the atom to which the substituent is attached

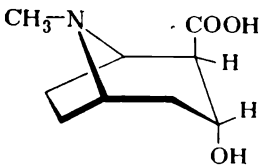
but also by the tropane skeleton as a whole (the atoms 1 and 5, which are pseudoasymmetric in tropane itself, assume true asymmetry). Such compounds exist in four stereoisomeric, optically active forms; this case is reminiscent of the stereoisomerism of borneol. If the ring of the thus substituted tropane has one more substituent at C-3, this atom too becomes asymmetric: the number of stereoisomers increases to 8, i.e., four pairs of optical antipodes. As an example may be cited ecgonine, the analogue of tropine, which has an extra carboxyl group in position 2. Below are given the formulas of the four stereoisomers of ecgonine (each of which has also an optical antipode with the formula which is the mirror-image of the one given below) and their names:



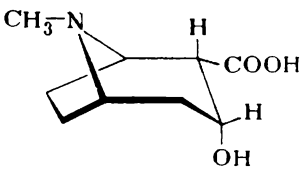

Ecgonine




Pseudoecgonine

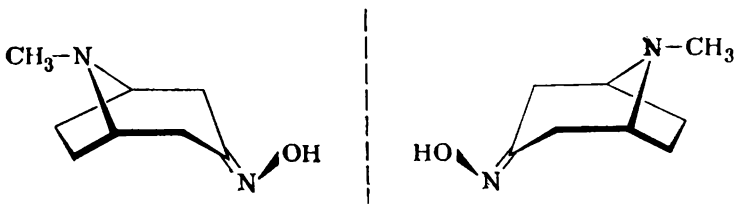



Alloecgonine




Pseudoalloecgonine

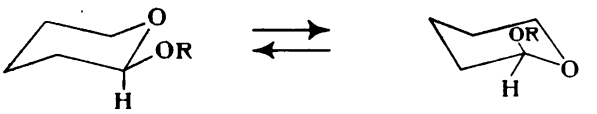
An interesting case of molecular asymmetry has been observed in the tropanone oxime (23). Tropanone itself is a symmetrical compound (the plane of symmetry passes through the nitrogen atom, carbon C-3 and the mid-point of the bond C-6—C-7). When converted into the oxime, because of the pyramidal structure of the oxime nitrogen the symmetry is disturbed and the existence of optically active forms becomes possible, just as in the oxime of N-methyl-2,6-biphenyl-4-piperidone considered earlier (see page 518):



## 8.5. THE ANOMERIC EFFECT

In the middle 1950's it was established for the first time that compounds of the pyran series do not always obey the conformational rules that operate in the cyclohexane series. This phenomenon was termed the **anomeric effect** and was studied thoroughly in subsequent years for monosaccharides and simpler pyrans (see ref. 24 for a review article).

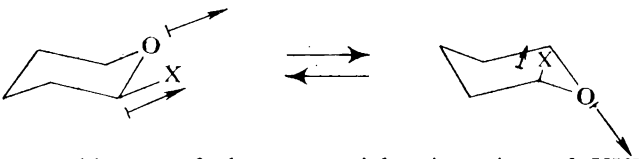
One of the simplest examples is 2-alkoxytetrahydropyran, for which two conformations are possible—with an equatorial and an axial substituent:



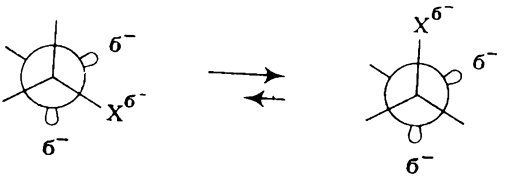

XVIIIa XVIIIb

One would think that equatorial conformation XVIIIa must be the preferred one, but, as a matter of fact, these compounds exist by 60-90 per cent in conformation XVIIIb with an *axial* alkoxy group.

The instability of the equatorial conformation is thought to be caused by the unfavourable orientation of the dipoles of the C—X bonds and of the cyclic oxygen (with account taken of the orientation of its free electron pairs):



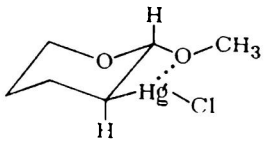

The unfavourableness of the equatorial orientation of XVIIIa (on the left in the scheme given below) becomes clearer when viewing the Newman projections along the bond $C_1$—O (the loops denote the free electron pairs of oxygen):



A study of the effect of the solvent on the equilibrium of the equatorial-axial forms of 2-methoxytetrahydropyran has shown that the fraction of the equatorial form increases with increasing dielectric constant since the dipole-dipole repulsion diminishes.

| Solvent | Dielectric constant | Percentage of equatorial form |
|---|---|---|
| Carbon tetrachloride | 2.2 | 17 |
| Deuterobenzene | 2.3 | 18 |
| Carbon disulphide | 2.6 | 20 |
| Deuterodimethyl sulphoxide | 36 | 26 |
| Deuterochloroform | 4.8 | 29 |
| $CH_3OD$ | 32 | 31 |
| Deuteroacetonitrile | 38 | 32 |
| Heavy water | 78 | 48 |

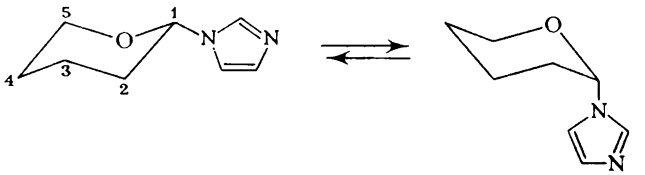
Zefirov examined the effect of the *third* substituent on the conformation of 2-alkoxytetrahydropyrans. For 2-methoxytetrahydropyran it has been found, from NMR spectral data, that the axial conformation is more preferable (80 per cent), which is a manifestation of the anomeric effect. Then 2-methoxy-3-chloromercuritetrahydropyran was studied and it was found that it exists in the equatorial conformation, i.e., no anomeric effect is displayed here. Incidentally, it is known that the conformational energy of the HgCl group is zero and, hence, it is *not* its tendency to occupy the equatorial position that leads to the change of the conformation. The authors explain the result obtained by the **coordination stabilization** of the equatorial conformation due to the interaction between oxygen and mercury:



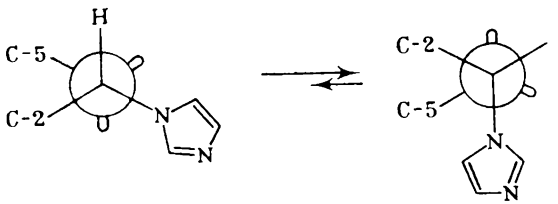

The anomeric effect has also been detected in nitrogen analogues—compounds of the piperidine series (25).

In those cases when the partial charge on a given substituent is found to be positive instead of negative, the direction of the operation of the anomeric effect is reversed. This **reverse anomeric effect** has been clearly

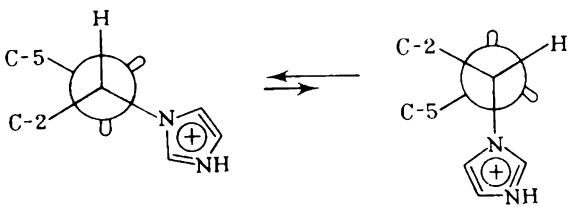
revealed in the investigation of N-glycosylimidazoles and their protonated forms.



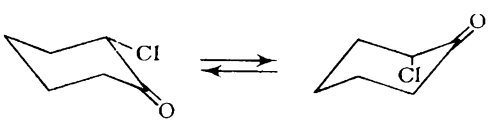
Anomeric effect



Reverse anomeric effect on protonation



A phenomenon closely related in character to the anomeric effect is the tendency for the halogen atom in 2-halocyclohexanones to occupy the axial position:

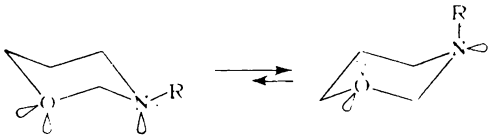


XIXa XIXb

In accordance with the ordinary rules of conformational analysis, the equatorial orientation of the halogen atom should have been the preferred one, but because of the same dipole-dipole interaction, as in compounds of the pyran series, the equatorial conformation XIXa is destabilized and conditions are created for the appearance of the axial conformation XIXb. The position of the equilibrium between the two conformations depends on the solvent used (see page 343).

If the six-membered ring contains two heteroatoms with free electron pairs in the 1,3-positions, the anomeric effect results in the predomina-

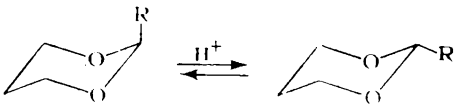
tion of a conformation in which there is no unfavourable parallel disposition of the orbitals of the free electron pairs on both heteroatoms:



The destabilizing effect of the parallel disposition of the free electron pairs in the left of the conformations given above is often called the "rabbit ear effect": it is commonly considered to be, in the long run, responsible for the anomeric effect. Recently, however, Zhdanov (26) came to the conclusion, on the basis of quantum-chemical calculations, that the anomeric effect is not the result of the steric or electronic repulsion between non-bonded atoms or of the interaction of polar bonds. In these authors' opinion, the anomeric effect is determined by the barriers to the rotation about a carbon-heteroatom bond and lends itself to description with the aid of semi-empirical quantum methods on the basis of this model.

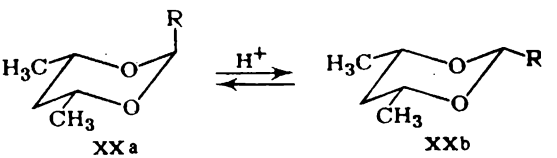
## 8.6. 1,3-DIOXANS

Eliel (27) has thoroughly studied the conformational equilibrium in the series of substituted 1,3-dioxans. These compounds are easily prepared from carbonyl compounds and glycols, and their NMR spectra can easily be interpreted. In acid medium, there is established a thermodynamic equilibrium between the axial and equatorial forms:



XXa XXb

Examination of this equilibrium allows one to determine the conformational energies of the substituents and to compare them with those found in cyclohexane and aliphatic compounds. For example, for the system XXa ⇌ XXb

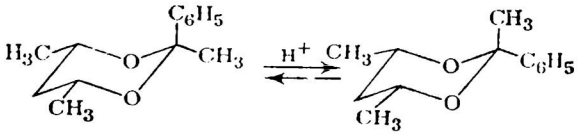


XXa XXb

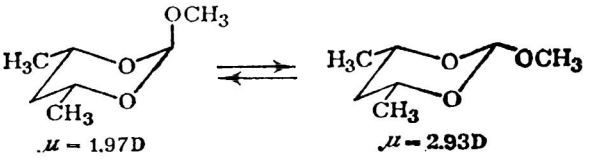
there have been found the following conformational free energies (the corresponding values for substituted cyclohexanes are given for comparison):

| R | $-\Delta G$ for substituted 1,3-dioxans XX, kJ/mole | $-\Delta G$ for substituted cyclohexanes, kJ/mole |
|---|---|---|
| $CH_3$ | 16.6 | 7.1 |
| $C_2H_5$ | 16.7 | 7.4 |
| *iso*-$C_3H_7$ | 17.3 | 9.0 |
| $C_6H_5$ | 13.0 | 12.6 |

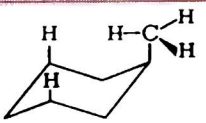
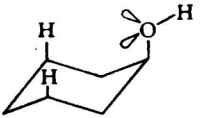
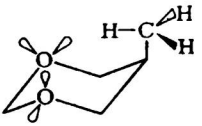
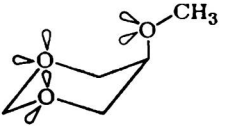
A point of interest here is the considerable increase of the conformational energy of the alkyl groups as compared with those observed for the cyclohexane series. This is accounted for by the fact that, because of the C—O bond lengths being smaller than the C—C bond length, the distance from R to the axial hydrogen atoms in positions 4 and 6 is smaller than the corresponding distance in substituted cyclohexanes. The low conformational energy of the phenyl group is also unexpected. The fact that in the 1,3-dioxan series it is really lower than the conformational energy of the $CH_3$ group is confirmed by the study of the conformational equilibrium of a ketal from *meso*-2,4-pentanediol and acetophenone:



The isomer with an *axial* phenyl group prevails at this equilibrium. The axial orientation is also favoured for the methoxy group, which has a direct relation to the anomeric effect; a convenient method of investigation in this case is the examination of the dipole moments.



Summarizing the data obtained, Eliel reports the following values of conformational energy as a function of the type of interaction:

| Type of interaction | Structure | Conformational energy |
|---|---|---|
| Atom-atom |  | 7.1 kJ/mole |
| Atom-electron pair |  | 2.5 kJ/mole |
| |  | 3.4 kJ/mole |
| Electron pair - electron pair |  | 0.0 kJ/mole |

## 8.7. 1,4-DIOXANS AND THEIR ANALOGUES

Like other six-membered rings, the molecule of 1,4-dioxan has the chair form (the boat form is by 9.2 kJ/mole less favourable). The barrier to the inversion of the chair form must be rather low since even at —104°C there has been observed no splitting of the signals in the PMR spectrum into the signals of the axial and equatorial protons.

In the molecules of *trans*-2,3- and *trans*-2,5-dihalogen-1,4-dioxans, which exist in the chair conformation, the halogen atoms have the *axial* orientation. This effect is analogous to the anomeric effect, i.e., we are dealing here with the interaction of the dipole of the C—X bond with that of the *p*-electrons of oxygen.

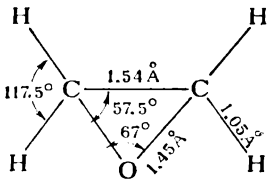
In the fused-ring system of benzodioxan, the heterocyclic ring has the half-chair form which is readily convertible (28).

**Piperazine** is the nitrogen analogue of 1,4-dioxan. Calculations show that the chair form of piperazine is by 16 kJ/mole more stable than the boat form. This conclusion has been experimentally verified in investigations of N,N′-dichloropiperazine carried out by the electron diffraction method. It has turned out that the chlorine atoms occupy the equa-

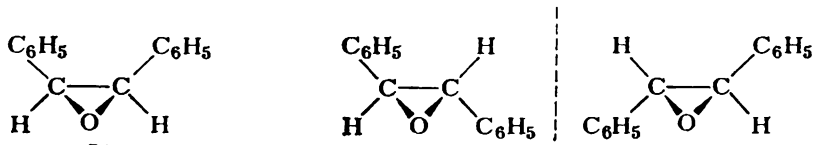
torial positions. Similar results have been obtained for piperazine itself, N,N'-dimethylpiperazine. The barrier to conversion for N,N'-dimethylpiperazine is 56±2 kJ/mole.

## 8.8. OTHER (NOT SIX-MEMBERED) OXYGEN-CONTAINING HETEROCYCLES

The simplest type of oxygen-containing heterocycles is **epoxides** (olefin oxides). These compounds are characterized by the following geometric parameters (ethylene oxide is taken as an example):

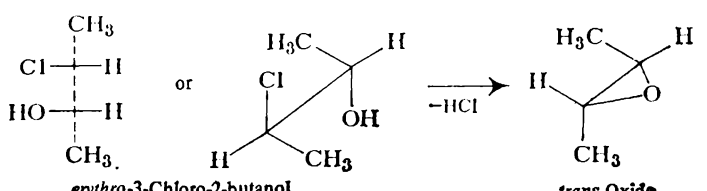


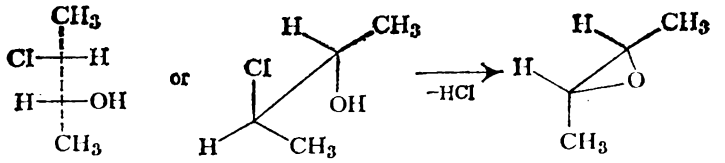

The existence of both geometrical and optical isomers is possible for substituted epoxides. An example is stilbene oxide:




Optical isomerism is also observed in monosubstituted epoxides; one example is propylene oxide.

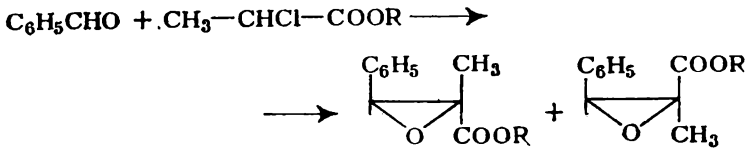
The most general route for the preparation of epoxides—the removal of hydrogen halide from halohydrins—is effected by the mechanism of a bimolecular substitution reaction with inversion of configuration at the carbon atom from which the halogen atom is removed. In this process, diastereomeric halohydrins give geometrically isomeric oxides; for example:



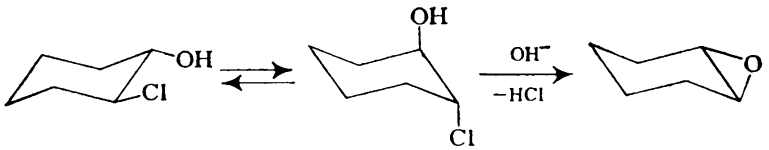



*threo*-3-Chloro-2-butanol · *cis*-Oxide

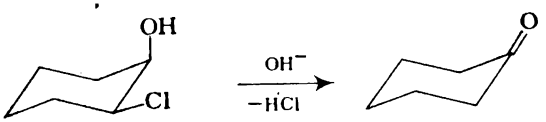
Stereoisomeric epoxides also result from the condensation of benzaldehyde with the esters of α-chlorosubstituted acids (the Darzen condensation); one example is (30):




In halohydrins of cyclohexane, the steric conditions required for epoxides to be formed are realized only in *trans*-isomers which react in the diaxial conformation:

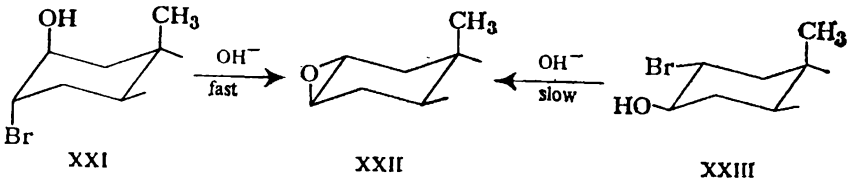



*cis*-Isomers in which it is impossible to create conformations with the required *trans*-diaxial arrangement of the groups participating in the reaction are slowly converted into ketones as a result of a hydride shift instead of giving epoxides:




Especially characteristic are the differences in reactivity between the halohydrins of the steroid series, in which the rigid polycyclic carbon skeleton completely removes the conformational mobility. The diaxial halohydrin 3α-bromo-2β-hydroxycholestane XXI when acted on by alkali is converted into epoxide XXII in the cold for 30 seconds, while

the diequatorial isomer 2α-bromo-3β-hydroxycholestane XXIII requires heating for 75 hours:




XXI XXII XXIII

Axial-equatorial isomers, for example, 3β-bromo-2β-hydroxycholestane when reacted with bases do not form epoxides at all and are converted (like the axial-equatorial halohydrins of cyclohexane) into ketones.

The stereospecificity of reactions leading to epoxides has been used for the synthesis of optically active propylene oxide by the following scheme (31):

$$\text{(—)-}S\text{-Ethyl lactate} \xrightarrow{LiAlH_4} \text{(—)-}S\text{-Propane-1,2-diol} \xrightarrow[CH_3COOH]{HBr}$$

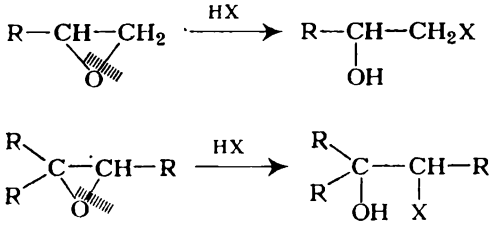
$$\longrightarrow \text{2-Acetoxy-1-bromopropane} \xrightarrow{C_5H_{11}OK} \text{(—)-}S\text{-Propylene oxide}$$

$$[\alpha]_D = -18.6°$$

(in chloroform)

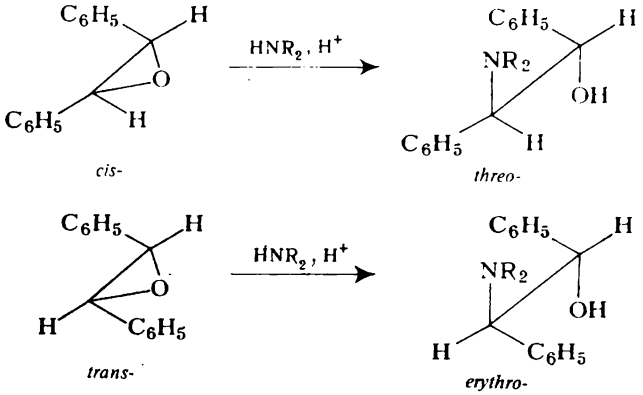
High stereospecificity is also characteristic of the Prilezhaev reaction in which epoxides are formed by the *cis*-addition of oxygen to the double bond.

The epoxide ring is known to be readily opened by the action of nucleophilic reagents. Like the formation of epoxides, this reaction proceeds by the $S_N2$ mechanism, the bond between the oxygen atom and the less substituted carbon atom being predominantly broken in accordance with the Krasussky rule:



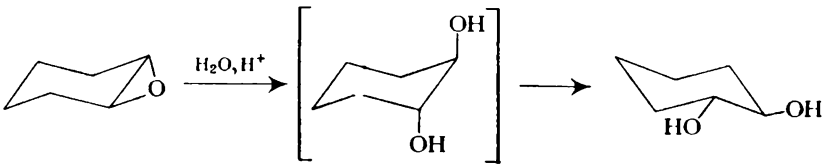

Stereochemically, the opening of the epoxide ring occurs, as should be expected for the $S_N2$ mechanism, with inversion of configuration at

the asymmetric centre disturbed during the course of the reaction, as, for example, in the case of stilbene oxides:

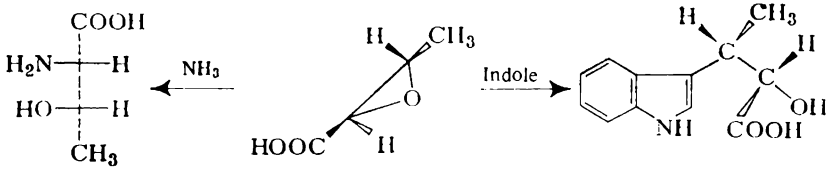



Accordingly, *cis*-2,3-epoxybutane on addition of water gives racemic 2,3-butanediol and *trans*-2,3-epoxybutane forms a *meso*-diol.

When the epoxides obtained from cycloalkenes are opened, *trans*-forms of disubstituted cycloalkanes are formed; for example:




The stereospecificity of the reactions of formation of epoxides and their ring-opening has repeatedly been used for correlation of configurations, as, for example, in the case of the following compounds (32):



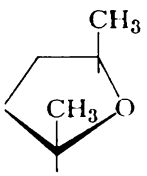

(+)-Allothreonine (configuration is known)

(−)-*trans*-2,3-Epoxybutyric acid

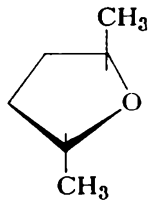
(−)-Indolmycin acid

The stereochemistry of reactions involving the opening of the epoxide ring has been reviewed in the literature (33).

Like other saturated heterocyclic compounds, substituted **tetrahydrofurans** can exist in *cis-trans*-isomeric forms, say, in the case of 2,5-dimethyltetrahydrofuran (34):



*cis*-,
b.p. 90-91°C;
$n_D^{20} = 1.4031$

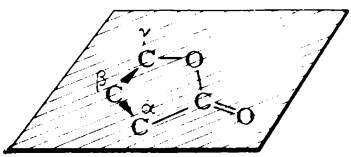


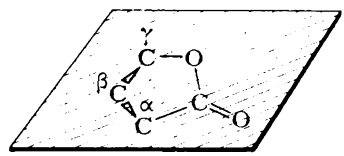
*trans*-,
b.p. 92-94°C;
$n_D^{20} = 1.4052$

The *trans*-form exists as a pair of optical antipodes.

A very curious phenomenon was observed when optically active tetrahydrofurans were mixed with cyclohexanone, acetone, or other achiral ketones: their absorption bands became almost optically active. This is an indication that a symmetrical chromophore may become optically active not only due to the intramolecular but also intermolecular effect of the asymmetric centre (35).

The five-membered oxygen-containing ring is also present in γ-lactones. The grouping $-\overset{\alpha}{C}-CO-O-\overset{\gamma}{C}$ exists predominantly in a planar conformation, while the β-carbon atom may lie either above or below this plane:

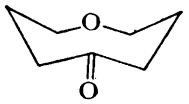




The sign of rotation of optically active lactones depends on their conformation (36).

The *eight-membered* oxygen-containing heterocycle of oxacycloocta-5-none, which exists in the twin-boat conformation XXIV, displays,

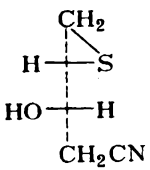
according to NMR spectral data, a transannular interaction between the ring oxygen and the carbonyl group (37):



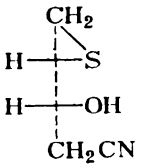
XXIV

## 8.9. SULPHUR-CONTAINING HETEROCYCLES

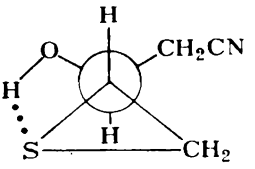
The three-membered sulphur-containing ring is encountered in compounds called **episulphides.** The regularities observed in the formation and ring-opening of these compounds are the same as in the epoxide series. Interesting features have been revealed by the study of the IR and NMR spectra of diastereomeric episulphides (38).



*threo-*



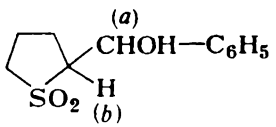
*erythro-*



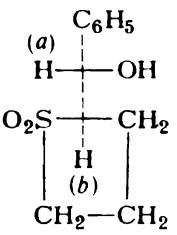
XXV

The *threo*-isomer is capable of existing in conformation XXV with an intramolecular hydrogen bond, but this conformation is unfavourable for the *erythro*-isomer in which intermolecular association predominates.

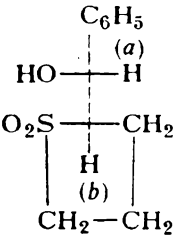
The diastereoisomerism of five-membered sulphur-containing heterocycles XXVI has been studied with the aid of NMR spectroscopy.



XXVI

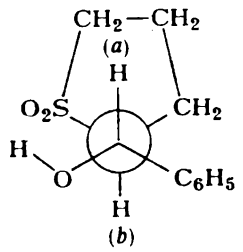


*threo-*



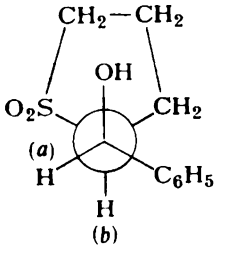
*erythro-*

Each of the diastereomers exists largely in a conformation in which the $SO_2$ group of the heterocyclic nucleus is at maximum distance from the phenyl group. The protons $\overset{(a)}{H}$ and $\overset{(b)}{H}$ are found to be at different distances from each other: their spin-spin splitting constants can be used to differentiate between the diastereomers (39):




*threo-*

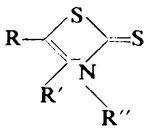
m.p. 159°C; $J_{(a)(b)}=9$ cps




*erythro-*

m.p. 97–98°C; $J_{(a)(b)}=2.2$ cps

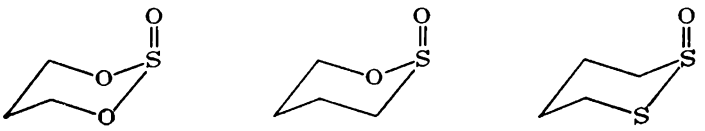
With five-membered rings containing sulphur and nitrogen, there has been observed the so-called **cogwheel effect**—the interaction of two groups attached to adjacent ring atoms:



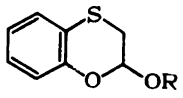

The conformations of the R′ and R″ groups are interdependent because the substituents "cogwheel" with each other on rotation about the bond linking them to the ring (40).

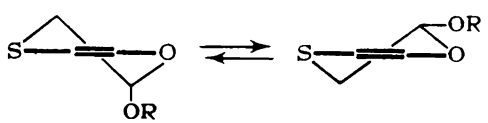
There is extensive material concerning *six-membered* sulphur-containing heterocyclic compounds. Tetrahydrothiapyran and its analogues, like other six-membered heterocycles, exist in the chair form. Compounds in which two sulphur atoms are next to each other (1,2-dithianes) are characterized by unusual values of barriers to the inversion of the chair form, of the order of 50 kJ/mole.

The preferred conformations for cyclic trimethylene sulphites and their analogues are conformations with an axially oriented S=O bond due to the manifestation of the anomeric effect; for example (41):



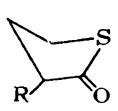
The anomeric effect reveals itself also in 2-alkoxybenzo-1,4-thioxanes which exist by 60-65 per cent in conformation XXVIIa with an axial alkoxy group (42):



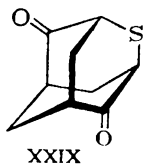


XXVIIa XXVIIb

Data on the conformations of thiol-γ-lactones XXVIII and also of the derivatives of thiaadamantane, say XXIX, have been obtained by means of the circular dichroism method (43):



XXVIII



XXIX

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CHAPTER 9

# Stereochemistry of Nitrogen

## 9.1. SPATIAL STRUCTURE OF THE AMINES

The stereochemistry of nitrogen originated from the work of Hantzsch and Werner published in 1890 and entitled "Concerning the Spatial Arrangement of Atoms in Nitrogen-Containing Molecules". For nitrogen-containing compounds, there were observed isomers, the existence of which could not be explained either by the difference in chemical constitution or the stereochemistry of the tetrahedral carbon atom. Extending logically the idea of van't Hoff, Hantzsch and Werner proposed a spatial model for the nitrogen atom. Like the tetrahedral model of the carbon atom, the Hantzsch-Werner model was later confirmed by physical methods.

It has been established, by means of electron diffraction studies, that the ammonia molecule has the configuration of a trigonal pyramid with the nitrogen atom situated at the apex; the geometrical parameters are shown in Fig. 9.1. The geometrical parameters of many organic compounds of tricovalent nitrogen have been determined (1), say, trimethylamine too has the structure of a trigonal pyramid with a valence angle at the nitrogen atom equal to 108.7°.

In compounds of tricovalent nitrogen, the central atom has a free electron pair; assuming it to be the "fourth substituent", we arrive at the structure resembling the conventional familiar model of the tetrahedral carbon atom. The "umbrella", however, is not stable: it can easily be turned inside out:

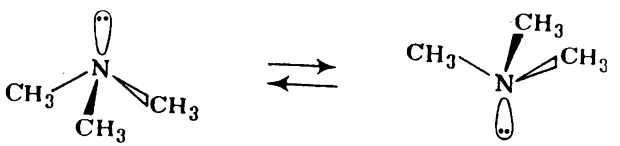
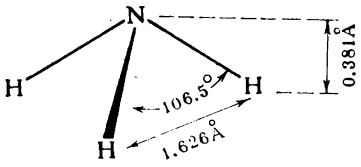


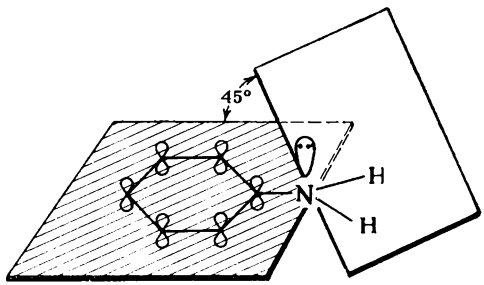
Figure 9.1.




*The geometrical parameters of the ammonia molecule.*

The stereochemical consequences of the inversion will be discussed at a later time (see page 562). At this point, we shall only note that the barrier to pyramidal inversion of nitrogen in amines is not high, being equal to 20-30 kJ/mole (2). The inversion barriers rise if, instead of the alkyl groups, nitrogen acquires substituents such as the halogen atoms, the hydroxyl group, the cyano group (3). Thus, for $(C_2H_5)_2NCl$ the inversion barrier is about 40 kJ/mole at —70°C. When the nitrogen atom is incorporated into a more or less long chain, as, for example, in triethylamine, there appears the possibility of existence of the molecule in various conformations; this question was already considered in Chapter 4 (see page 253).

The nitrogen atom retains the pyramidal structure in aromatic amines as well. For example, in aniline (4) the angle between the planes containing the benzene ring and the $NH_2$ group is 45°.




With this angle, the free electron pair of nitrogen is oriented in parallel to the $\pi$-electron system of the aromatic nucleus, which provides conjugation.

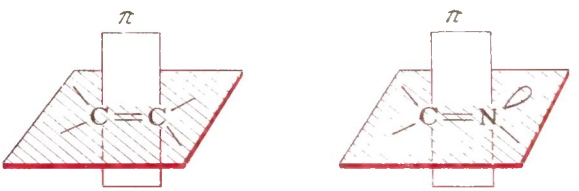
Compounds of the triphenylamine type exist in the form of the pyramidal "three-bladed propeller" (5), though, one would think, with the

*planar* conformation there could be attained the conjugation of the free electron pair with all the rings.

## 9.2. GEOMETRICAL ISOMERISM OF THE OXIMES

The stereoisomerism possible for compounds with the N=C and N=N double bonds resembles the geometrical isomerism of ethylenic compounds.

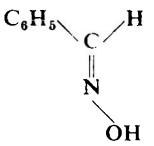
In compounds in which nitrogen forms a double bond, the third valency of nitrogen is found to be at an angle to the plane of the double bond. The geometrical picture is quite the same as in ethylene compounds, only one substituent being absent; instead, a free electron pair is present.



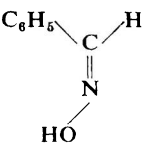

If the carbon of the carbon-nitrogen double bond is linked to two different substituents (X and Y), the substituent Z attached to nitrogen may be on one side of the plane of the π-bond either with substituent X or with substituent Y. Thus, there appears the possibility of existence of *geometrical isomers* similar to the *cis-trans* isomers of ethylene compounds.

In order not to confuse this type of stereoisomerism with the ordinary *cis-trans* isomerism, use is made of the special terms *syn* and *anti*. The *syn-anti* isomerism has been most thoroughly studied for oximes.

It is precisely the existence of isomeric forms of oximes, which cannot be explained from the standpoint of either structure theory or the stereochemistry of the carbon atom, that served at one time as an impetus for the creation of the Hantzsch-Werner theory. Such isomers were first observed in 1883 by Goldschmidt for benzil dioxime (dibenzoyl dioxime). Similar isomers exist for benzaldoxime:



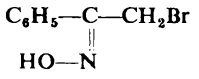

I. *syn*-Benzaldoxime
m.p. 34°C



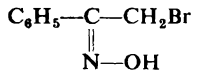

II. *anti*-Benzaldoxime
m.p. 128-130°C

The terms *syn* and *anti* in the case of aldoximes mean the nearness (or, accordingly, remoteness) of the hydrogen atom and the oxime hydroxyl group. The isomeric benzaldoximes differ not only in physical but also chemical properties. Whereas *syn*-benzaldoxime gives an acetyl derivative under the action of acetic anhydride, the *anti*-oxime under the same conditions loses the elements of water, being converted into a nitrile. The difference in physical properties between *syn*- and *anti*-isomers allows their separation by crystallization and various chromatographic methods (6).

The oximes of symmetrical ketones (e.g., benzophenone) have no isomers; the oximes of unsymmetrical ketones are capable of existence as two stereoisomers; for example (7):



III. m.p. 114°C

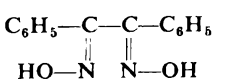


IV. m.p. 97°C

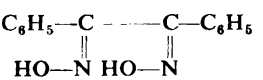
For ketoximes the *syn-anti* symbolism is inconvenient since one has to indicate the radical with respect to which the hydroxyl group is in the *syn*- or *anti*-position. Therefore, for the configurations of the oximes to be designated unambiguously, use is often made of the Z,E-system (see page 35) in which the priority of substituents is determined by the calculation of atomic numbers according to the Cahn-Ingold-Prelog rule. The letter Z corresponds to the *cis*-arrangement of highest-priority groups, and the letter E, to their *trans*-disposition. The stereoisomers of the oximes mentioned above are named as follows:

I = E-benzaldoxime
II = Z-benzaldoxime
III = E-ω-bromoacetophenone oxime
IV = Z-ω-bromoacetophenone oxime

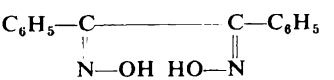
The oximes of symmetrical diketones exist in three stereoisomeric forms, for example:



*anti*-Benzil dioxime
(E,E-benzil dioxime)



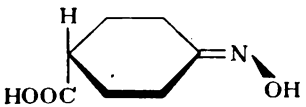
*amphi*-Benzil dioxime
(E,Z-benzil dioxime)



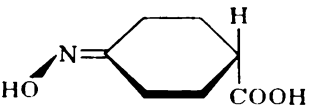
*syn*-Benzil dioxime
(Z,Z-benzil dioxime)

If the radicals in a diketone are different, its dioximes can now exist in four stereoisomeric forms. As an example may be cited the oximes of camphorquinone.

An investigation into the stereochemistry of the oximes has made it possible to obtain purely chemical evidence for the spatial position of substituents around the nitrogen atom. What is meant here is the investigation carried out in 1910 by Mills, which provided a direct experimental proof that in the group $\rangle C{=}N-$ the third valency of nitrogen does not lie in the plane of the double bond. To do this, Mills prepared oxime V from cyclohexanonecarboxylic acid. The structure becomes asymmetrical and two optical antipodes appear only because the third valency does not lie in the plane of the double bond:

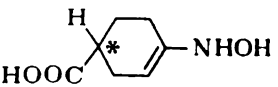



Va

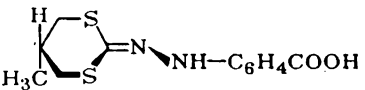



Vb

There was, however, a certain probability that the oxime exists in the tautomeric form and optical activity is produced simply as a result of the presence of an asymmetric carbon atom:




To exclude this possibility, Mills later synthesized an optically active oxime of the type VI. There were, at a later time, produced other compounds, whose asymmetry is due to the same specific features of the spatial structure of oximes (see Chapter 8, page 518).



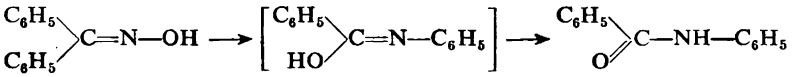

VI

Just as in the case of the *cis-trans* isomerism of ethylenes, one of the forms of oximes *(syn-* or *anti-)* is usually more stable; both these forms are interconvertible. The transition from the labile to the stable form sometimes occurs spontaneously, more often on heating or under the

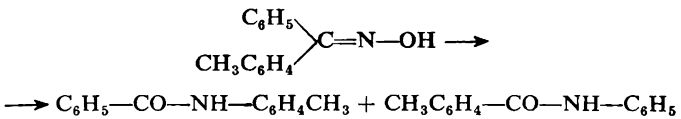
action of chemical reagents (acid, halogens, etc.). Thus, *anti*-benzaldoxime when reacted with sulphuric or hydrochloric acid and also with bromine is converted into *syn*-benzaldoxime. *m*-Nitrobenzaldoxime undergoes the analogous transformation under the action of light.

How can the configuration of the oximes be determined, i.e., how can it be established, for example, which of the benzaldoximes—with a melting point of 34°C or 130°C—is the *syn*- and which is the *anti*-form?

The configurational relationships of the oximes were originally elucidated in connection with the **Beckmann rearrangement** (or *Beckmann transformation*). The result of this rearrangement is the conversion of an oxime into an amide, a process that can formally be represented as the interchange of one of the radicals of a ketone and the hydroxyl group with the subsequent transformation of the imine to the amide form:



In the course of the Beckmann rearrangement, the stereoisomeric oximes give different products. Thus, structurally isomeric amides are obtained from the two stereoisomeric forms of phenyltolyl ketoxime:

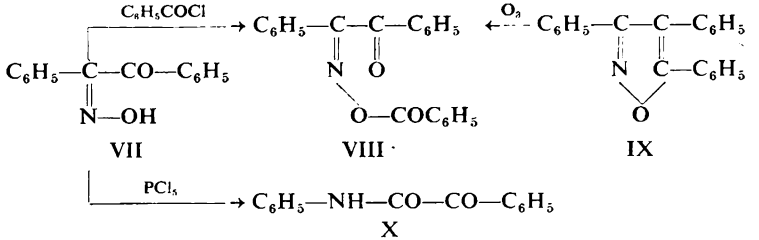


These isomeric amides can also be obtained through the migration of either the radical $C_6H_4CH_3$ or $C_6H_5$ to the nitrogen atom.

In the 1890's, Hantzsch advanced the assumption (which seemed "natural" at the time) that the exchange occurred between the closely spaced groups, i.e., the radical that is in the *syn*-position to the hydroxyl group migrates to the nitrogen atom according to Hantzsch. The "logic" of this interpretation did not cause any doubts, and the structure of the products of the Beckmann rearrangement has been for a long period of time the only tool for determination of the configuration of oximes. Nobody noticed that there was a fundamental error: the steric centre does not remain intact during the course of the rearrangement and therefore there is no certainty that the configuration is retained during the reaction.

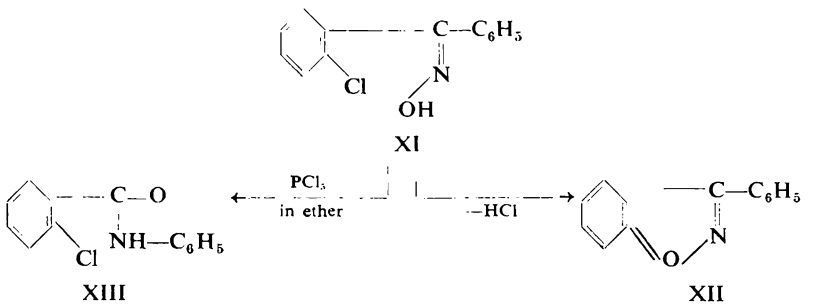
The first attempt to determine the configuration of the oximes without the use of the Beckmann rearrangement was undertaken by Meisenhei-

mer in the early 1920's. To do this, he effected and compared the following transformations:



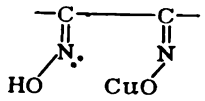

Triphenyliso-oxazole IX was subjected to ozonolysis to give the O-benzoyl derivative of *anti*-phenyl benzilmonoxime, VIII. According to the method of preparation, in this compound the benzoylated oxime hydroxyl group must be in the *syn*-position relative to the radical —CO—$C_6H_5$. Compound VIII was also prepared by a different method—by way of the benzoylation of the so-called β-form of the dibenzoyl monoxime (*anti*-phenyl benzilmonoxime); this allows configuration VII to be assigned to this compound. This conclusion is based on the fact that in the conversions IX → VIII and VII → VIII the C=N double bond remains intact and, hence, the configuration about this bond is not changed. In the Beckmann rearrangement, however, the oxime VII gave the anilide of phenylglyoxylic acid (X), and this means that the hydroxyl group and the radical in the *anti*-position to it are exchanged.

The configuration of *o*-chlorobenzophenone oxime XI has been established on the basis of the following: compound XI readily loses hydrogen chloride with the formation of the benzoxazole derivative XII; this is an indication of the spatial closeness of the chlorine atom to the hydroxyl group (the steric centre remains intact in this reaction!). In another reaction, in the course of the Beckmann rearrangement, the oxime XI forms the anilide of *o*-chlorobenzoic acid (XIII). Hence, in this case too there takes place an *anti*-exchange:

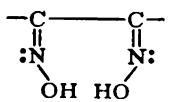


It has been firmly established at present that the *trans*-exchange (the *anti*-exchange) is the general regularity for the **Beckmann rearrangement** (though there are cases where this rearrangement proceeds non-stereospecifically, i.e., both possible amides are formed). The conception of which of the aldoximes readily eliminates water to form nitriles has also been revised: this elimination too proceeds more readily from the *anti*-position.

To determine the configurations of aldoximes and ketoximes, use may also be made of their ability to form inner-complex (chelate) structures. Of the stereoisomeric dioximes, it is the form in which two functions (the oxime hydroxyl group and the electron pair on the adjacent nitrogen atom) can interact that is capable of forming chelates:

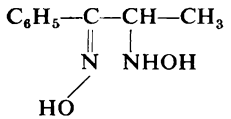


Chelate ring is formed

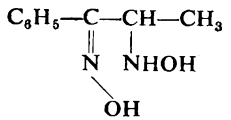


No chelate ring is formed

A further example of the use of the reaction leading to the formation of chelate rings is provided by α-hydroxylaminoximes, the configurations of which have been elucidated in an analogous way (8):

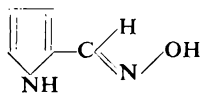


m.p. 164-166°C; forms chelate complexes with copper and iron

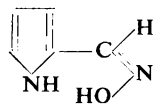


m.p. 156-158°C, forms no complexes

The heterocyclic nitrogen atom may serve as the second functional group required for the formation of the chelate ring, as has been demonstrated in the determination of the configuration of the oximes of pyrrolealdehydes (9):



m.p. 70°C, forms a chelate complex

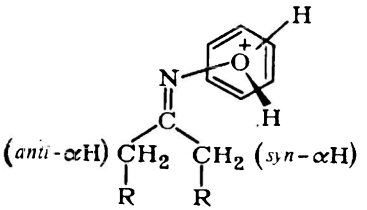


m.p. 164°C, forms no chelate complex

Of the physical methods the following were used to determine the configuration of the oximes: determination of solubility and dipole moment measurements. A review article covering the literature on this

question up to 1933 has been written by Blatt (10). At present, of primary importance for determination of the configuration of the oximes is nuclear magnetic resonance (NMR) spectroscopy, several variants of which are used for this purpose. For example, the configuration of an oxime may be deduced from the magnitude of chemical shift of the signal of the proton of the OH group (11); use may also be made of NMR on $^{15}N$ nuclei (12):

If an oxime is dissolved in benzene containing traces of hydrogen chloride, there can be observed shifts of the signals from protons in the α-position to the orginal carbonyl group. The signals of α-protons which are in the *syn*-position to the oxime hydroxyl group are shifted to the side of the strong fields, whereas the signals of the *anti*-α-protons shift to weak fields. This result is believed (13) to be associated with the formation of complexes in which the α-protons in the *syn*- and *anti*-positions are fixed at different distances from the benzene ring and undergo different chemical shifts under the influence of this ring:

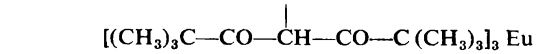



The following data on the percentage content of the *syn-anti* forms of aliphatic aldoximes and ketoximes have been obtained by means of NMR spectroscopy (14):

| R | R′ | Content of *syn*-, % | Content of *anti*-, % |
|---|---|---|---|
| H | $CH_3$ | 39 | 61 |
| H | $C_2H_5$ | 56 | 44 |
| H | $CH(CH_3)_2$ | 73 | 27 |
| H | Cyclopentyl | 64 | 36 |
| H | Cyclohexyl | 70 | 30 |
| $CH_3$ | $C_2H_5$ | 74 | 26 |
| $CH_3$ | $C_6H_5$ | 94 | 6 |
| $CH(CH_3)_2$ | $C(CH_3)_3$ | 100 | 0 |

These results should have been expected on the basis of the simplest steric considerations: as the size of the substituent increases the configuration in which this substituent is close to the hydroxyl group becomes less and less favourable.

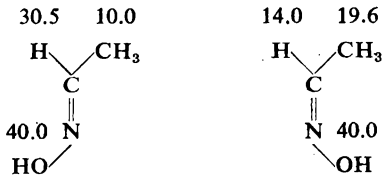
The PMR method with the use of shift reagents such as europium dipivalylmethanate [Eu(dpm)$_3$]



has proved especially effective in this respect.

This complex is capable of additionally coordinating with compounds having functional groups with free electron pairs. The PMR spectra of the organic compounds contained in the complex undergo substantial changes. The magnitude of the signal shift depends on the distance between the europium atom (i.e., the coordination site) and the corresponding proton. In the case of oximes this means that the signals of the radicals in the *syn*-position to the hydroxyl group are found to be shifted from their normal positions more strongly than the signals of the radicals in the *anti*-position.

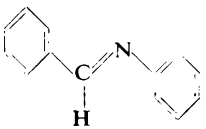
If the procedure with benzene and hydrogen chloride makes use of hundredth (sometimes, tenth) fractions of ppm, then, when europium complexes are employed, the shifts are stronger; for example (15) (below are given the values of $\Delta\delta = \delta - \delta_0$ which is the difference between the chemical shifts $\delta$ in the presence of an equimolar amount of the europium complex and $\delta_0$ which denotes chemical shifts observed without addition of the complex):



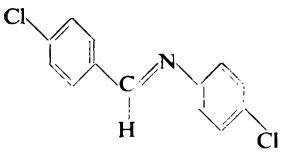

## 9.3. STEREOCHEMISTRY OF SCHIFF'S BASES

As early as 1894 there were described two forms of Schiff's base (anils) prepared from aniline and acetaldehyde, which differed in melting point and solubility; this was accounted for by the existence of the *syn-anti* isomers:

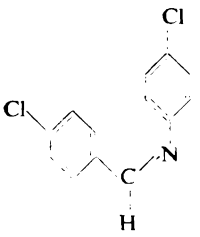
Later, on the basis of the study of the dipole moments, English investigators came to the conclusion that the Schiff's bases produced from substituted benzaldehydes and substituted anilines exist in the *anti*-form. This conclusion was drawn from the coincidence of the dipole moments of benzilideneaniline XIV and *p*-chlorobenzilidene-*p*-chloroaniline XV. Such a coincidence is possible only in those cases where the dipoles of C—Cl bonds are pointing in space in different directions and cancel out on vectorial addition. Such a direction of C—Cl bonds is present in the *anti*-form XVa but not in the *syn*-form XVb.




XIV

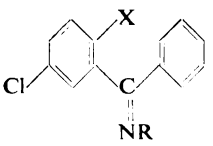



XVa




XVb

More recent works showed that the equilibrium of the *syn-anti* forms can be observed for ketimines, and in certain cases, these forms can also be isolated in the individual state. Thus, the *syn-anti* forms of the ketimines of substituted benzophenones XVI were separated by fractional crystallization (16).

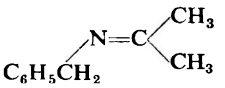



XVI

The configurations of the isolated stereoisomers were determined by means of ultraviolet, infrared and NMR spectroscopy. Note that stereoisomeric forms of this kind may be regarded, because of their low stability, both as conformers and as stereoisomers, and, accordingly, either the

conformational equilibrium or the readily interconvertible stereoisomeric forms are spoken of in the literature.

The principle of the application of NMR spectroscopy for determination of the configuration (conformation) of Schiff's bases will be considered below for the case of acetone benzylimine, the methyl groups of which are diastereotopic and give separate signals in the NMR spectrum (17):

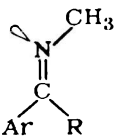



δ 2.02

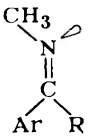
δ 2.86

These signals do not merge on heating up to 170°C, indicating that up to this temperature the stability of the configuration is retained. For acetone anil, $C_6H_5—N=C(CH_3)_2$ the signals merge at 140°C, i.e., the *syn-anti* isomerization occurs somewhat more readily. Thus, using the NMR method, one can detect the existence of the *syn-anti*-isomeric forms of ketimines even in those cases when it is impossible to isolate them, to obtain data on the percentage content of the forms in the equilibrium mixture, and to estimate their stability.

For the conformational equilibrium of Schiff's bases obtained from methylamine and aromatic carbonyl compounds XVII (18)




XVII a
E-Form




XVII b
Z-Form

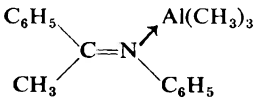
the following data have been obtained by means of NMR spectroscopy (measurements in deuterochloroform at 35°C):

| Ar | R | Content of XVIIa, % | Content of XVIIb, % |
|---|---|---|---|
| $C_6H_5$ | H | 100 | 0 |
| $C_6H_5$ | $CH_3$ | 93 | 7 |
| $C_6H_5$ | $C_2H_5$ | 74 | 26 |
| $C_6H_5$ | $C_3H_7$ | 70 | 30 |
| $C_6H_5$ | $CH(CH_3)_2$ | 5 | 95 |
| $C_6H_5$ | $C(CH_3)_3$ | 0 | 100 |
| *o*-$CH_3OC_6H_4$ | $CH_3$ | 42 | 58 |

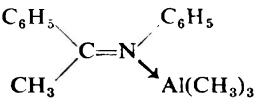
Consideration of the first six compounds shows that as the size of the substituent increases its unfavourable interaction with the $CH_3$ group is enhanced and the fraction of the E-form (XVIIa) decreases. A comparison of the second and seventh compounds XVII, R = $CH_3$, Ar = = $C_6H_5$ and XVII, R = $CH_3$, Ar = $C_6H_4OCH_3$-*o* shows that the *ortho*-substituents in the benzene ring and the electronic effects also exert an influence: the increase of the electron density in the ring of methoxy derivative XVII, R = $CH_3$, Ar = $C_6H_4OCH_3$-*o*, increases the repulsion between the aromatic ring and the electron pair of nitrogen, reducing the fraction of the E-form as compared with the unsubstituted compound XVII, R = $CH_3$, Ar = $C_6H_5$.

Analogous data on the equilibrium of the Z,E-forms have been obtained for Schiff's bases prepared from α-phenylethylamine and methyl alkyl ketones (19).

The position of the equilibrium of the stereoisomeric forms is influenced by the presence of complex-formers. Thus, for example, N-(α-methylbenzilidene)-aniline exists usually in the E-form; the $CH_3$ group in this form gives a signal at 1.96 ppm. On gradual addition of trimethylaluminium this signal is attenuated and is somewhat shifted and a signal at 2.65 ppm appears simultaneously and is amplified. In the presence of 1 mole of $(CH_3)_3Al$ both signals assume the same intensity: the two forms exist under these conditions (20):

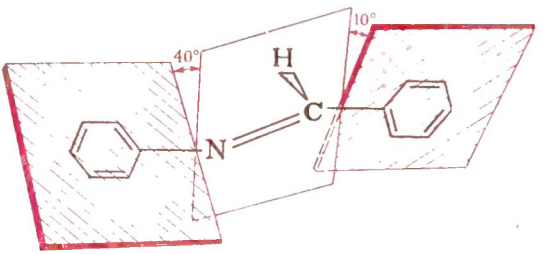



$\delta_{CH_3}$ = 1.87 ppm
Complex of the E-form



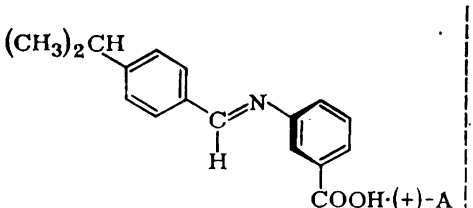

$\delta_{CH_3}$ = 2.65 ppm
Complex of the Z-form

The authors of numerous works have come to the conclusion that the benzene rings of aromatic Schiff's bases are buckled out of the plane in which the C=N double bond lies (21).

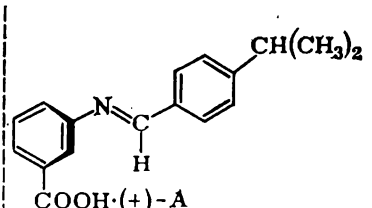



Minkin and coworkers (22) paid attention to the fact that such structures with *ortho*- or *meta*-substituents have no elements of symmetry and, hence, should exist

in optically active forms. To check up this conclusion, these authors obtained such a Schiff's base in the form of a salt with optically active α-phenylethylamine [designated by (+)-A in the formulas given below]. The observed mutarotation of the salt with increase of the negative rotation was explained by the establishment of an equilibrium between the diastereomers XVIII and XIX:



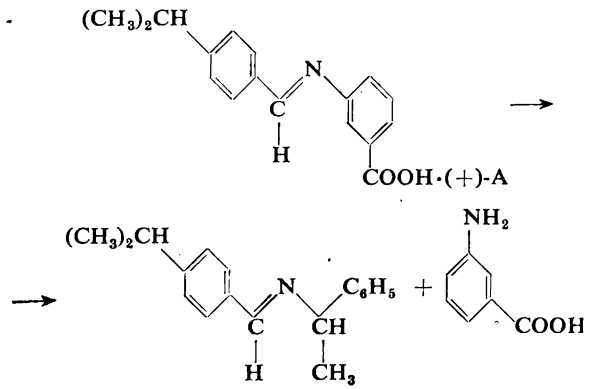

XVIII




XIX

The structures of Schiff's bases XVIII and XIX, as shown above, are indeed antipodes (the second moiety of the molecule, optically active (+)-α-phenylethylamine, is the same in both cases; therefore, as a whole, XVIII and XIX are *diastereomers*). However, by rotation about the bond between the aromatic ring and the nitrogen atom both structures coincide. Hence, for stable antipodes of this type to exist, it is necessary that no rotation occur about this bond. The fixing of the conformation may be associated, however, with the weak conjugation of the π-electrons of the aromatic ring with the free electron pair of nitrogen. This, however, does not exclude the possibility that in the presence of optically active (+)-α-phenylethylamine there will actually be predominantly separated from the solution one of the diastereomers, XVIII or XIX, the one which is less soluble; when it is dissolved there is then established an equilibrium between the two diastereomers, which manifests itself outwardly as mutarotation.

Another explanation must, however, be considered too: the gradual conversion into a compound of a different structure due to the replacement of the amine moiety in a Schiff's base.

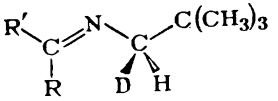



In this process, the negative rotation should also have been increased since such Schiff's bases obtained from (+)-α-phenylethylamine possess a strong left-handed rotation. An attempt to detect, by means of NMR spectroscopy, the diastereotopic

nature of the protons of the isopropyl groups in compounds of the type under consideration (i.e, to confirm the chirality of the imines) has failed (23).

As a whole, the question of a "new type of optical stereoisomerism" requires an additional study.

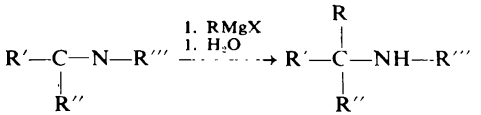
It is believed that the chirality of an "internally asymmetric chromophore" is responsible for the unusually high values of rotation of optically active imines of the type XX. The specific rotation $[\alpha]_D$ reaches 3.8-5.4°, which is about 20 times greater than the rotation of amines with deuterium asymmetry, from which these Schiff's bases have been obtained (24).



XX

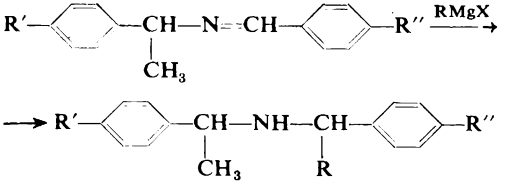
The authors of a number of works have noted the regularities relating the sign of rotation of Schiff's bases (25) or their optical rotatory dispersion curves to the configuration of the starting amines. In a series of works Smith (26) studied the salicylidene derivatives of the amines, which have especially high rotation values due to the formation of an internally asymmetric chromophore (owing to chelation).

Under the action of organomagnesium or organolithium compounds Schiff's bases are converted into secondary amines:

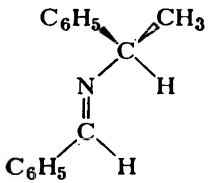


This gives rise to an asymmetric carbon atom. If the radical of the starting amine, R‴, in its turn, has had asymmetry, the reaction results in the formation of a mixture of diastereomers (a mixture of the *threo*- and *erythro*-forms). A number of works have been devoted to the study of the steric course of such reactions. As an example, let us consider a series of investigations carried out by Terentiev and coworkers (27).

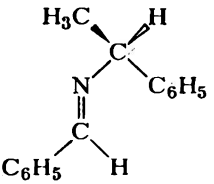
These authors have studied Schiff's bases obtained from α-phenylethylamine (or its ring-substituted analogues) and aromatic aldehydes:



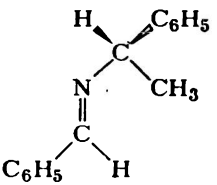
The analysis of the composition of the mixture of diastereomeric amines was conducted by means of gas-liquid chromatography. The results obtained are in agreement with the following model. It is known that aldimines have the E-configuration (see page 550); they exist in three conformations:



XXIa



XXIb



XXIc

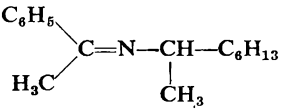
In conformation XXIa, the azomethine grouping lies in the plane of the drawing and so does the hydrogen atom situated next to the asymmetric centre of α-phenylethylamine. The configuration of the asymmetric centre formed in the reaction depends on the direction from which the radical from the organomagnesium compound approaches the carbon atom of the azomethine group—from behind the plane of the drawing or from the observer's side. The approach of the radical R from behind the plane of the drawing is blocked by the $CH_3$ group and that from the observer's side, by the $C_6H_5$ group; it is obvious that the approach from behind the plane of the drawing is more favoured in this conformation. The same refers to conformation XXIb, whereas for conformation XXIc the approach from the observer's side is more favourable. The approach from behind the plane of the drawing results in the formation of the *erythro*-form, and that from the observer's side gives the *threo*-form. Assuming that all the three conformations are equally probable, one can predict the preferred formation of the *erythro*-form; its fraction must increase with increasing size of the radical R. It is this result that has been obtained experimentally:

| R | $CH_3$ | $C_2H_5$ | $CH(CH_3)_2$ | $CH_2CH(CH_3)_2$ |
|---|---|---|---|---|
| *Erythro-*, % | 50 | 55 | 64 | 72 |
| *Threo-*, % | 50 | 45 | 36 | 28 |

The stereochemistry of such reactions has been investigated by other authors as well (28). Diastereomeric mixtures are also formed as the result of the reduction of ketimines obtained from amines with a chiral

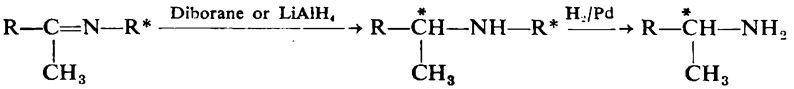
centre (29). As known, ketimines exist in the form of mixtures of *syn-anti* forms. It has turned out that the fractions of the *threo-* and *erythro-*forms of amines coincide with the equilibrium content of the *anti-* and *syn-*forms in the starting ketimine, respectively.

An analogous work has been carried out with the ketimine

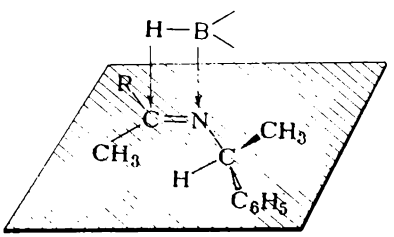


which exists by 87 per cent in the *anti-*form (with the bulky radicals being far apart). This ketimine gives a mixture of diastereomers, which contains 66 per cent of racemate (30).

The hydrogenation of Schiff's bases obtained from aliphatic ketones and optically active α-phenylethylamine (its residue is denoted by R*) has been found to give first diastereomeric secondary amines and then, after the removal of the α-phenylethylamine residue, optically active primary amines:

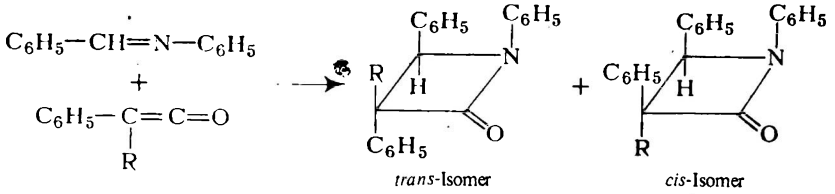


The optical purity of the thus produced amines is 30-60 per cent. In the opinion of the authors of the work in question, the reaction conformation may be pictured as follows:



The preference of this conformation is determined by the fact that the closest to the $CH_3$ group of the ketone fragment is the smallest of the substituents at the asymmetric centre, i.e., the hydrogen atom. The hydrogen responsible for the hydrogenation approaches from above, being blocked by the $CH_3$ group of the asymmetric centre, whereas the approach from below would be hampered by the phenyl group (cf. the consideration of XXIa on page 555).

The addition of ketoketenes to Schiff's bases with the formation of four-membered rings also proceeds stereospecifically (32). For example:

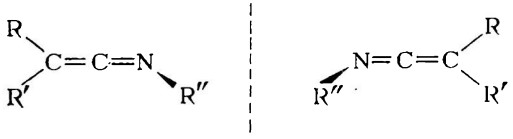



In this reaction, the corresponding *cis*- and *trans*-isomers are formed in the following proportion:

| R | *trans*, % | *cis*, % |
|---|---|---|
| H | 100 | 0 |
| $CH_3$ | 80 | 20 |
| $C_2H_5$ | 33 | 67 |
| $CH(CH_3)_2$ | 10 | 90 |

Thus, as the size of the radical R increases its disposition on the same side with the phenyl group becomes increasingly unfavourable, and the isomer with the *cis*-arrangement of the two phenyl groups begins predominating in the reaction products.

A peculiar spatial structure is shown by **keteneimines**: their cumulated double bonds create conditions for the existence of optical antipodes resembling those of allenes (33):



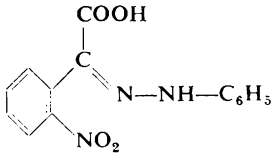

The barrier to racemization is not high: 40-50 kJ/mole, and such optical antipodes are therefore difficult to isolate.

In conclusion, it remains to note that, apart from *syn-anti* isomerism, a number of Schiff's bases have been found to exhibit tautomerism in the form of the reversible transformation to the enamine form (34).

## 9.4. OTHER CASES OF STEREOCHEMISTRY OF A DOUBLY BONDED NITROGEN

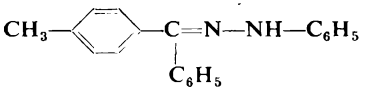
The *syn-anti* isomerism is known to be exhibited by a number of other compounds containing the grouping $\diagdown C{=}N-\diagup$. Such compounds include numerous derivatives of aldehydes and ketones: hydrazones, phenylhydrazones, semicarbazones, etc. These cases of *syn-anti* isomerism have been, however, studied considerably less thoroughly than the stereoisomerism of the oximes and Schiff's bases and we shall therefore limit our consideration to only a few examples.

The *syn-anti* isomerism in the series of **phenylhydrazones** was first observed as early as 1890 by Krause who studied the phenylhydrazone of *o*-nitrophenylglyoxylic acid (XXII), which was obtained in two modifications.

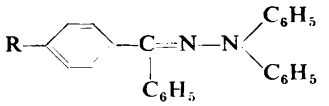



XXII

A convenient method of preparing the *syn-anti* isomers of phenylhydrazones is by the action of phenylhydrazine not on ketones but on the corresponding dihalogeno derivatives with halogen atoms linked to one carbon atom (*gem*-dichlorides). In this way, there have been obtained, in particular, phenylhydrazones in two forms, XXIII and XXIV:




XXIII

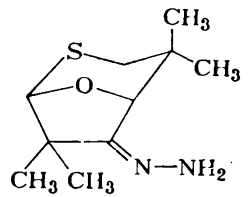



XXIV, R = $CH_3$ or $OCH_3$

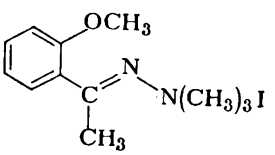
Compounds XXIV are interesting in that they have no hydrogen atom linked to the nitrogen atom and, hence, the possibility of tautomeric changes is excluded. The existence of two forms can therefore be explained only by the *syn-anti* isomerism with respect to the $\diagdown C{=}N-\diagup$ bond.

**Hydrazones** can exist in geometrically isomeric forms which are readily interconvertible. Thus, for example, the hydrazone of trifluoroacetone

exists exclusively in a conformation with the *anti*-arrangement of the $CF_3$ and $NH_2$ groups (35). Only in rare cases could the stereoisomeric forms of hydrazones be separated (36):

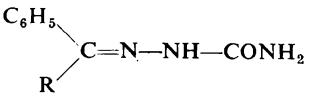


Two forms, m.p. 127 and 151°C; the barrier to *syn-anti* isomerizations is 130 kJ/mole

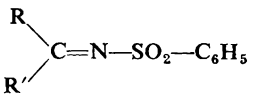


Two forms, m.p. 140 and 158°C

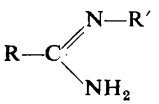
*syn-anti*-Isomerism has also been found to be exhibited by other compounds with a double carbon-nitrogen bond; for example:



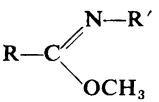
Semicarbazones (37)



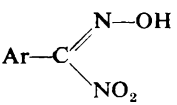
Benzenesulphonylimines (38)



N-Alkylamidines (39)



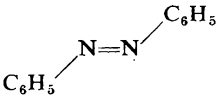
N,O-Dialkylimidates (40)



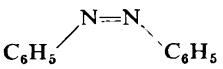
Arylnitrolic acids (41)

The concept of *syn-anti* isomerism can also be extended to the model of the nitrogen-nitrogen double bond. One of the simplest compounds

of this type is azobenzene, which should be expected to have two isomers:



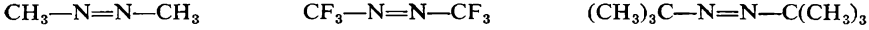
XXVa, *anti-*



XXVb, *syn-*

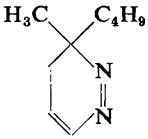
Only one azobenzene has long been known to exist, the one with a melting point of 68°C, which is isomorphic with *trans*-stilbene and has no dipole moment. It was because of these properties that the *trans*-structure XXVa was assigned to azobenzene. The second isomer (the *syn*-form with m.p. 71°C and a dipole moment of 3 D) was isolated from "ordinary" azobenzene (the *anti*-form) by irradiating it with ultraviolet light.

The simplest aliphatic azo compound, azomethane XXVI, has the *anti*-configuration, while the trifluoromethyl analogue XXVII has the *syn*-configuration. The equilibrium of the *syn-anti* forms has been detected for an azo compound with *tert*-butyl radicals, XXVIII (42).

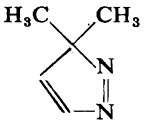


XXVI XXVII XXVIII

Ultraviolet spectroscopy has proved to be a good method for studying the conformations of cyclic azo compounds since the position of the absorption band of the azo group depends on the N=N—C valence angle:

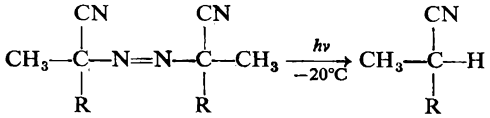


$\lambda_{max}$ = 435 nm



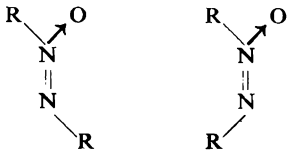
$\lambda_{max}$ = 335 nm

Azonitriles were used to demonstrate the retention of optical activity in the photolysis products of azo compounds (44):



According to the IR spectral data, the starting azonitriles exist in the *anti*-configuration (45).

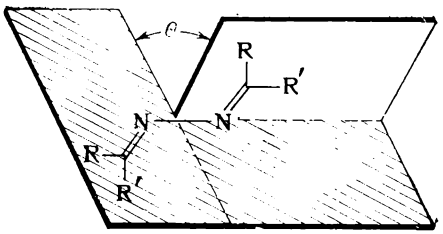
In accordance with their formula, azoxy compounds may also be expected to have geometrical isomers:



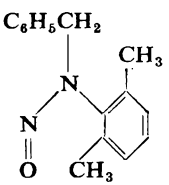
The isomerism of these compounds was studied in the 1930's by Müller in his detailed works. He succeeded in isolating the stereoisomeric forms and in proving their structure and configuration by means of ultraviolet spectra and dipole moments.

The **azines** of aldehydes and ketones (46) exist in a conformation with imine fragments in different planes. The angle θ varies between 20 and 70°, depending on R.

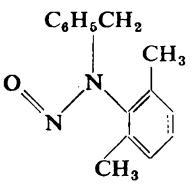
$$RR'C{=}N{-}N{=}CRR'$$



A peculiar case—the existence of stable *conformers* that are formed due to restricted rotation about the nitrogen-nitrogen *single* bond—has been described for nitrosamines (47):



XXIX



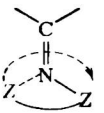
XXX

Chromatographing on silica gel makes it possible to prepare the individual conformers XXIX and XXX which differ in physical characteristics:

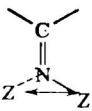
| | $\delta_{CH_2}$ | $\delta_{CH_3}$ | $R_f$ | m.p., °C |
|---|---|---|---|---|
| XXIX | 5.51 | 1.74 | 0.4 | 62-63.5 |
| XXX | 4.91 | 1.89 | 0.6 | 86.5-88 |

The conformers are stable in the crystalline state; on melting or in solution there is established an equilibrium with the form XXX predominating; the barrier to interconversion is about 100 kJ/mole.

Stereoisomers with a C=N double bond are in principle interconvertible by rotation about the C=N double bond or else by pyramidal inversion — the "turning-inside-out of the umbrella" (the umbrella effect) just as is the case with ammonia and amines:




Isomerization by way of rotation

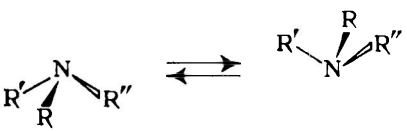



Isomerization by way of inversion

The data available provide evidence in favour of the inversion.

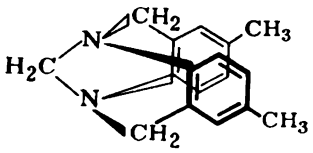
## 9.5. OPTICAL ACTIVITY OF COMPOUNDS OF TERVALENT NITROGEN

The pyramidal model of the ammonia molecule makes one to assume that tertiary amines of the type RR′R″N, which have no elements of symmetry, must exist in optically active forms. Many attempts have been made to prepare such optically active compounds but they all have failed. Antipodes of this type are too readily interconverted by pyramidal inversion (for a review article see ref. 48):



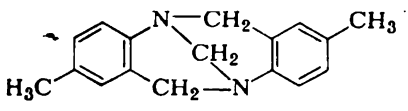

If the nitrogen atom is contained in the ring, its configuration is fixed more firmly. The first example of this type of optical activity was described in 1944 by Prelog, who succeeded in obtaining the so-called

Tröger's base in an optically active form (by chromatographing on lactose); it has the spatial structure XXXI (the structural form XXXII):

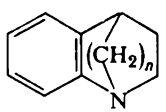


XXXI

The nitrogen atom becomes asymmetric in other bridged compounds as well, say, in XXXIII (49):

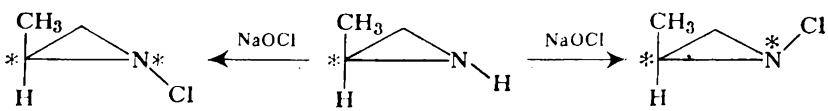


XXXII



XXXIII

Configurational stability is also acquired by compounds in which the nitrogen atom is incorporated into a small, rigid ring. As an example may be cited the ethylene-imines (aziridines) studied in the works of Kostyanovsky (50). The starting compound used in these studies was optically active 2-methylaziridine XXXIV, a compound whose optical activity is associated with the presence of an ordinary asymmetric carbon atom. The action of hypochlorite led to the formation of an N-chloro derivative which was obtained in two forms differing in the configuration about the nitrogen atom:



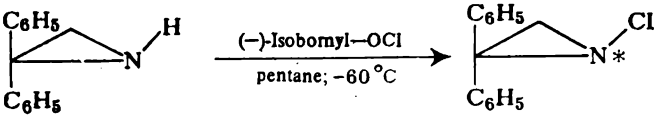

*trans*- Form
$[\alpha]_D = +94°$

XXXIV
$[\alpha]_D = -8.1°$

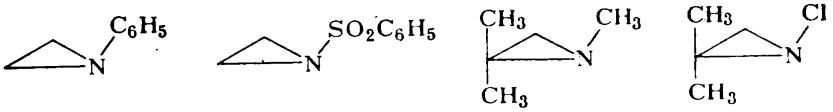
*cis*- Form
$[\alpha]_D = -81°$

Thus, it has been shown, for the first time, that the nonbridged nitrogen atom too is capable of retaining the stability of its pyramid and of escaping inversion in certain compounds.

Another route to optically active aziridines is by the action of optically active hypochlorite on an aziridine (51):

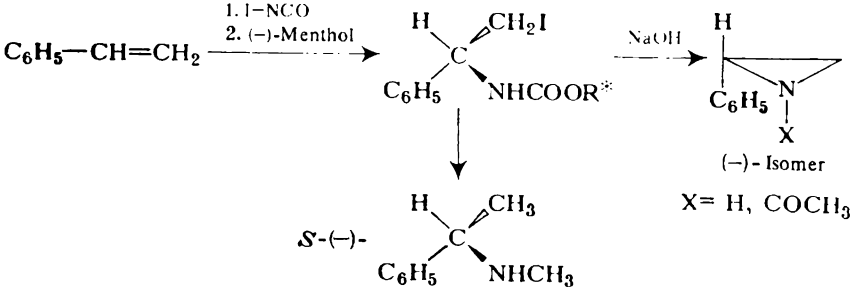



In the compound obtained, the only factor responsible for optical activity is the asymmetric nitrogen atom, whereas in the compounds prepared by Kostyanovsky there was an asymmetric carbon atom too. The energy barriers to inversion for aziridines of different structure are as follows:




47 52 78 100 kJ/mole

The configuration of the asymmetric carbon centre of phenylaziridine has been elucidated by its correlation with α-phenylethylamine according to the scheme (52):

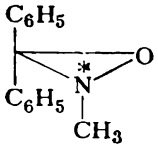



The stereochemistry of the opening of the aziridine ring has also been studied: just as in the case of epoxides, the reaction proceeds by the *trans*-scheme.

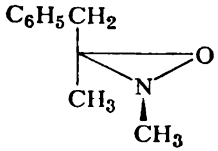
Optical activity is also displayed by 2-methyl-3,3-diphenyloxaziridine XXXV as a result of retarded inversion. The authors (53) who prepared this optically active compound spoke of *molecular* asymmetry,

which is incorrect: this is, in fact, a case of the true asymmetric pyramidal tervalent nitrogen *atom*.

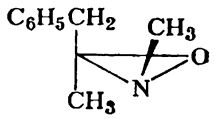
In those cases when the carbon atom of the oxaziridine ring bears two different substituents, geometrical isomerism becomes possible (54), say, in the case of compounds XXXVI. Each of the geometrical isomers can be resolved into optical antipodes.



XXXV

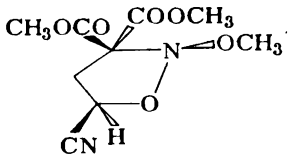


XXXVIa

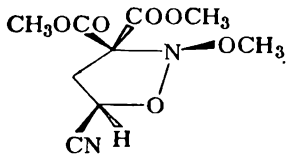


XXXVIb

Related structures with a five-membered ring also exhibit configurational stability. For the series of N-substituted 3,3-dimethylpyrrolidines the inversion barrier is 30-55 kJ/mole; just as with aziridines, it increases when halogens and the hydroxyl group are added to the nitrogen atom (55). In isolated cases, the barrier is high enough to allow the isolation of the individual stereoisomers. Thus, for example, the stereoisomers XXXVIIa and XXXVIIb were separated by chromatography on silica gel (56); at room temperature they are rather stable the equilibrium sets in upon the expiration of several weeks):

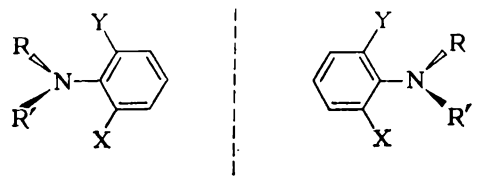


XXXVIIa



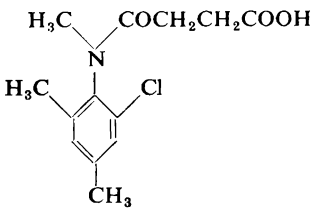
XXXVIIb

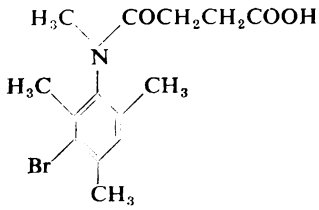
Tervalent nitrogen can also be used to build optically active compounds with restricted rotation about the single bond, which are similar to biphenyl derivatives:



The substituted amino group and the aromatic ring are arranged in perpendicular planes: there arises molecular asymmetry which resem-

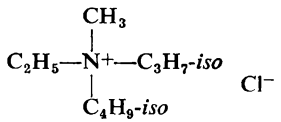
bles optically active biphenyls. Compounds of this type were studied by Adams, beginning from the 1940's. Two examples are given here:



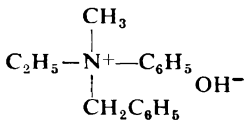


## 9.6. OPTICAL ACTIVITY OF COMPOUNDS OF FOUR-COORDINATE NITROGEN

The ammonium nitrogen with its four tetrahedrally arranged substituents is similar to the $sp^3$-hybridized carbon in stereochemical respect. In accordance with this, the tetracovalent (four-coordinate) nitrogen can serve as a chiral centre, as was demonstrated in 1899 in the preparation of optically active compounds XXXVIII and XXXIX:

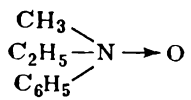


XXXVIII

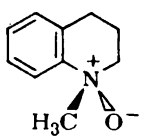


XXXIX

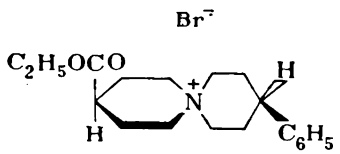
The oxides of amines with the nitrogen atom having the tetrahedral configuration have also been obtained in optically active forms (113), say, XL and XLI:



XL



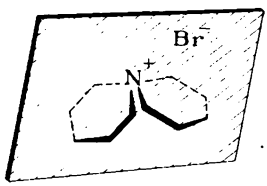
XLI



XLII

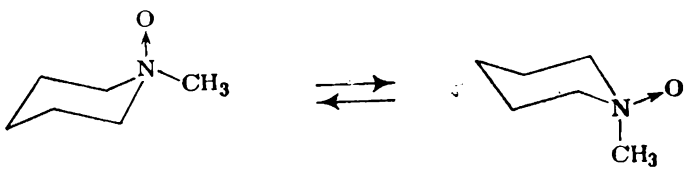
The ammonium nitrogen is also known to exhibit a stereoisomerism of the spiran type (e.g., compound XLII). The work aimed at preparing this compound was carried out by Mills in 1925 with the purpose of

proving the tetrahedral structure of the ammonium nitrogen since at the time, apart from this structure, the possibility of the pyramidal structure was also disputed. The point is that the optical activity of compounds XXXVIII-XLI is compatible both with the tetrahedral and the pyramidal model, but the asymmetry of the spiran XLII is possible only with the tetrahedral arrangement of the substituents about the nitrogen atom, whereas in the pyramidal structure XLIIa there would be a plane of symmetry passing through the nitrogen atom and the groups opposite to it:



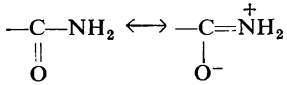

XLIIa

The conformational energy of inversion of the piperidine chair form has been found for the N-oxide of N-methylpiperidine (57); it proved to be equal to 5 kJ/mole.

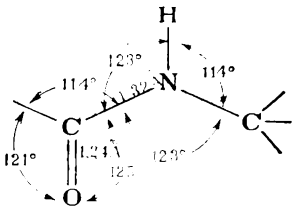



## 9.7. STEREOCHEMISTRY OF THE AMIDES

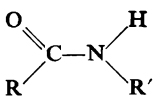
An interesting and peculiar chapter of stereochemistry is provided by the works devoted to the investigation of the spatial structure of the amides. The amide group is known to be one of the examples of mesomeric structures with extreme formulas:



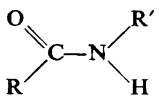
Mesomerism manifests itself, in particular, in a change of the valence angles and bond lengths:




All the three substituents at the nitrogen atom of the amides are arranged in one plane. The carbon-nitrogen bond in amides is shorter than the C—N single bond, and the carbon-oxygen bond is, on the contrary, longer than the carbon-oxygen double bond. The double-bond nature of the carbon-nitrogen bond creates a certain barrier to rotation about it and there appears the possibility of existence of two planar conformations:




Cisoid conformation
(E)



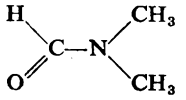

Transoid conformation
(Z)

It is custom to determine the cisoid or transoid arrangement in mono-substituted amides by the relative position of the carbonyl oxygen atom and the hydrogen atom attached to nitrogen. This notation requires a different approach in the case of disubstituted amides, since they become less spectacular. It is more convenient to designate the configurations for amides of any structure by using the Z,E-system; it is this system that will be used further in the text. Being, in principle, conformers, the Z,E-forms of amides are nevertheless found to be stable enough not only to be detected by means of physical methods but also to be isolated as individual substances in certain cases.

The examination of the details of the structure of the amide group was stimulated, in the first place, by the fact that this grouping is the basic unit of the structure of the polypeptide chain of proteins (see Chapter 11, page 617). However, since the 1960's, there have been published many works devoted to the spatial structure of simpler amides too. The decisive role in the study of the conformations of amides is played by NMR spectroscopy. The material accumulated has been summed up by Stewart and Siddall (58).

In one of the simplest amides, dimethylformamide, because of the restricted rotation about the C—N bond the formally identical methyl

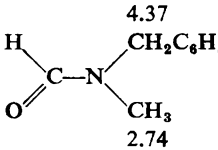
groups are found to be in different environments and have therefore somewhat differing chemical shifts (the data given below refer to a solution in $CCl_4$):

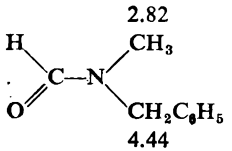



2.92 ppm

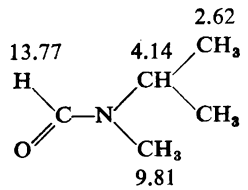
2.78 ppm

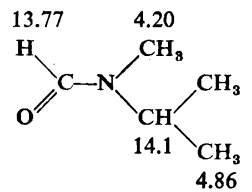
On heating up to the **coalescence temperature** both signals merge into one; this means that the rotation about the carbon-nitrogen single bond becomes sufficiently fast (on the time scale of the NMR method). A study of the temperature dependence of the NMR spectra permits calculating the barriers to rotation about C—N bonds. If there are different substituents attached to nitrogen, their chemical shifts will be different for both conformers. An example is N-methyl-N-benzylformamide (below are indicated the chemical shifts on the δ-scale at the corresponding groups):




Comparing the integral intensity of the corresponding signals of both conformers, one can determine the position of the conformational equilibrium. However, because of the low difference between the chemical shifts, accurate results can be obtained only on instruments of 100 or even 220 mHz. And in this case too, the use of shift reagents proved to be useful (such reagents were mentioned in discussing the stereochemistry of oximes; see page 549). When europium complexes are added, the differences between the $CH_3$ signals in dimethylamides are no longer tenths of a ppm but amount up to 5 ppm (if the molar amide-complex ratio is 1 : 1). The differences between the signals of the two conformers of unsymmetrically substituted amides also increase, accordingly. The shifts of the signals relative to their normal position (without addition of europium complexes) are, for example, as follows (in ppm):



Just as always in such cases, the stronger shift is observed in protons situated in the *syn*-position to oxygen and, accordingly, closer to the coordination site.

### 9.7.1. MONOSUBSTITUTED AMIDES

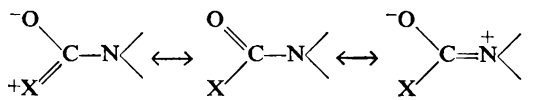
The simplest representatives of alkylamides are the monalkylated amides of formic acid. The following conformations are possible for them:

E-form Z-form

As the size of the radical increases its unfavourable steric interactions with the carbonyl oxygen are enhanced and the fraction of the Z-form is decreased. Thus, the fraction of the Z-form in the conformational equilibrium is (according to NMR spectral data) 92 per cent with R = $CH_3$, 88 per cent with R = $C_2H_5$, 80 per cent with R = *iso*-$C_3H_7$, and 82 per cent with R = *tert*-$C_4H_9$. The rotational barrier $\Delta G$ for *tert*-butylacetamide is 80 kJ/mole; in the case of the trimethylsilyl analogue it decreases down to 68 kJ/mole, which is accounted for by a *p-d* electronic interaction.

The monoalkylamides of acetic acid with any alkyl groups exist in the Z-form, i.e., with the transoid arrangement of the carbonyl oxygen and of the hydrogen atom linked to nitrogen. The barrier to rotation about the C—N bond for acetamide is 71 kJ/mole; for the monoalkylamides of acetic acid it is about 84 kJ/mole. A conclusion was made in studying the IR spectra of the monamides of the homologues of acetic acid that groups not larger than the ethyl and the isopropyl group may be in the cisoid position relative to each other.

In considering **acylated anilines,** apart from the volume of the substituent, a number of steric and electronic factors must also be taken into account, namely: the interaction of the acylamino group with the aromatic ring (the tendency for the free electron pair of the nitrogen atom to be coplanar with the π-electronic system of the aromatic ring); the steric interaction of *ortho*-substituents (including hydrogen atoms!) with the acylamino group; the bipolar repulsion between the π-electronic systems of the benzene ring and the carbonyl group. In general, when the amide group is linked to a radical capable of interacting mesomerically with it, one can predict the participation of three forms:



XLIIIc XLIIIa XLIIIb

If X is a substituent that tends to donate its electrons to give rise to the form XLIIIc, the contribution of the form XLIIIb will decrease as a result of the competition and so the barrier to the rotation about the C—N bond will also diminish (59).

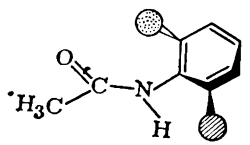
The simplest of this class of compounds, formanilide XLIV (R = H), in a solution of deuterochloroform at a concentration of 52 mol. per cent and at 35°C is in the Z-conformation by 73 per cent; on dilution the fraction of this form decreases and is 45 per cent at a concentration of 1.5 mol. per cent.

XLIV

Z-form E-form

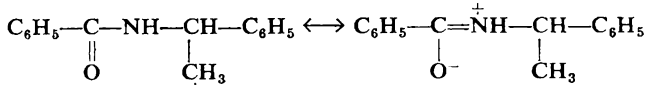
In estimating the causes of such a concentration dependence it was assumed that either the solvated E-form is thermodynamically more stable than the solvated Z-form or the E-form is stabilized even at low concentrations at the expense of hydrogen atoms contributing to the formation of cyclic dimers, while the Z-form is less liable to form analogous hydrogen bonds.

Acetanilide XLIV (R = $CH_3$) in pyridine solution exists almost exclusively in the Z-conformation. The presence of *ortho*-substituents in the benzene ring increases the size of the aryl group and leads to a certain shift of the conformational equilibrium to the side of formation of the E-form. This shift, however, is slight and the Z-form remains to be predominating: if acetanilide consists of the Z-form by 99 per cent, then under similar conditions 2-methylacetanilide exists in the Z-form by 94 per cent, 2-*tert*-butylacetanilide, by 75 per cent, and 2,4,6-tri-*tert*-butylacetanilide by 55 per cent. The fact that *ortho*-substituents have a relatively weak effect on the position of the conformational equilibrium is associated with the possibility of creation (due to the rotation about the N—aryl bonds) of such conformations in which the benzene ring is turned perpendicularly to the plane of the amide group and so the *ortho*-substituents are remote from the oxygen atom:



But if the *ortho*-position to the amide group of acylated anilines is occupied by a substituent capable of functioning as an acceptor of the proton of the hydrogen bond, the benzene ring is fixed in the plane of the amide group. Some authors believe that such an interaction occurs even between the *ortho*-hydrogen atom of the aromatic ring and the oxygen of the amide group.

In studying optically active amides of the benzoyl-α-phenylethylamine type it has been found that the solvent has a strong effect on the course of the ORD curves in the near UV region (60). A detailed examination of the effect of the solvent led to the assumption of the relation between these changes of the ORD curves and the shift of mesomerism to the side of one of the extreme forms (61):



The experimental data obtained in these studies were confirmed by Djerassi and Skulsky (62), though these authors advanced a different explanation of the phenomena observed. In subsequent years, the study of the solvent effect was continued with many other compounds of the amide type. Amides of a somewhat different structure—the anilides of α-halogenopropionic acids—were studied by means of the circular dichroism method (63).

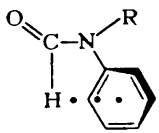
### 9.7.2. DISUBSTITUTED AMIDES

Disubstituted formamides exist predominantly in a conformation with the larger group in the transoid position to the carbonyl oxygen. In going from the disubstituted amides of formic acid to the analogous derivatives of other acids, not only the unfavourable steric interaction of the larger group with the oxygen atom (in the Z-conformation) but also the analogous interaction of the larger group with the radical of the acid moiety of the amide (in the E-conformation) begin to exert an influence on the preferred conformation. Therefore, the fraction of the E-conformation in such amides is smaller than in the corresponding formamides. For example, in the methylethylamides of formic and acetic acids, the fraction of the E-conformation is, respectively, 60 and 49 per cent; for the methylisopropylamides, these figures are 67 and 42 per cent, respectively.

For dimethylamides of various acids there have been found the barriers to rotation about the C—N bond: $\Delta G^{\neq}$ is 91 kJ/mole for dimethylformamide, and for the dimethylamide of acetic acid it is somewhat lower.

The *ortho*-substituents in benzamides increase the rotational barrier considerably: for example, for the dimethylamide of benzoic acid $\Delta G^{\neq}$ is 94 kJ/mole (at 168°C) and for the dimethylamide of 2,4,6-tri-*tert*-butylbenzoic acid it is about 130 kJ/mole (at 200°C). Such a high barrier makes possible the separation of the Z- and E-forms of such amides (see below).

Disubstituted amides with an aromatic substituent at nitrogen, N-methylformanilide and N-ethylformanilide, exist almost exclusively (by 95 per cent) in the E-conformation with the transoid arrangement of the carbonyl oxygen and the phenyl group. Such a conformation is accounted for not only by the more favourable steric arrangement (the more bulky substituent, the phenyl group, is remote from oxygen) but also by the formation of a hydrogen bond between the formyl proton and the π-system of the aromatic ring:

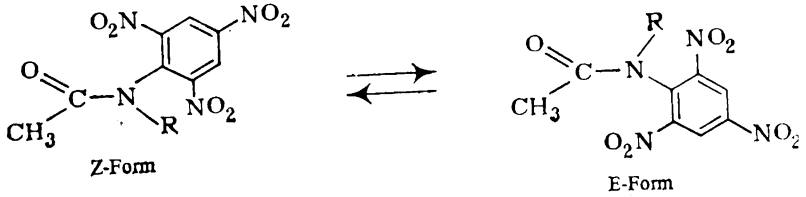



$R=CH_3,\ C_2H_5$

Of importance here is also the fact that the second possible Z-conformation is destabilized due to the repulsion between the π-electronic systems of the CO group and the aromatic ring.

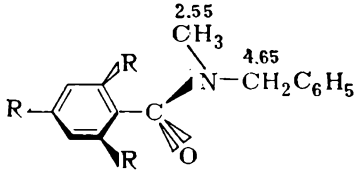
The alkylanilides of other acids also exist in the E-conformation.

Acylated picramides have been used (64) to study the effect of the second substituent at nitrogen on the conformation around the C—N bond. As should be expected, with increasing size of this substituent the fraction of the E-conformer with the transoid arrangement of the $CH_3$ and R groups increases:

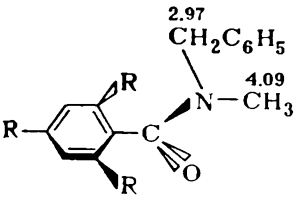



A rather high barrier to rotation about the C—N bond made it possible to prepare, in the individual state, the pure Z- and E-conformers of *o*-methylformanilide and 2,4,6-tri-*tert*-butylacetanilide; in the latter case, the separation was effected by means of thin-layer chromatography

at +5°C; $\Delta G^{\neq}$ was 100 kJ/mole at 185°C. The isomeric forms were isolated also in the series of acyl derivatives of benzylamine (65); for example (the magnitudes of chemical shifts of the groups are given in ppm):




m.p. 116–118°C



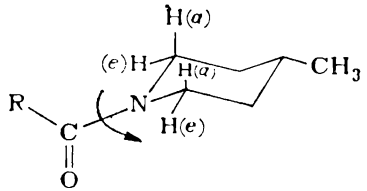

m.p. 152–154°C

$R = C(CH_3)_3$

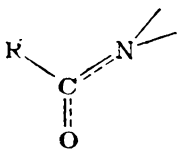
The conformers were separated by crystallization and thin-layer chromatography. The unusual stability of these conformers is associated with the fact that for the interconversion to be effected it is necessary to overcome not only the usual barrier to rotation about the partially double-linked C—N bond but also the steric hindrances created by the bulky *tert*-butyl groups. The *tert*-butyl groups are separated by the radical $CH_3$ in one of the conformers and by the residue $CH_2C_6H_5$ in the other. Thus, the amide mesomerism is supplemented here by atropisomerism reminiscent of the isomerism of biphenyl derivatives or substituted anilines.

### 9.7.3. N-HETEROCYCLIC AMIDES

In the case of the N-acylpiperidines studied by Johnson (66), the mesomerism of the amide group is combined with the possibility of existence of a six-membered ring in various conformations. For instance, in N-acetyl-4-methylpiperidine, at a temperature above 70°C there is observed a free rotation about the N—COR bond, as a result of which the α-hydrogens give two signals in the NMR spectrum, which correspond to the axial and equatorial orientation (XLVa).



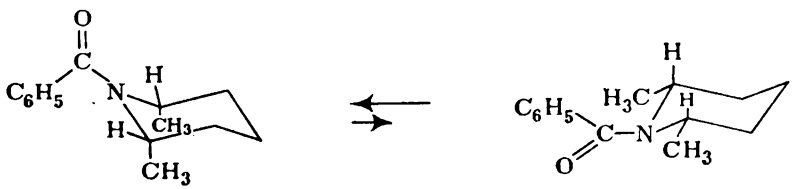

XLVa



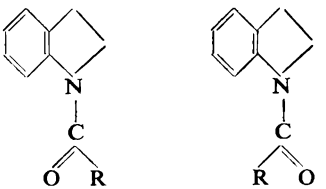

XLVb

At a temperature below 70°C the free rotation is stopped and there appears a planar system, XLVb, in which the α-hydrogens are in different magnetic environments and, accordingly, the number of signals from these hydrogen atoms in the NMR spectrum increases to four.

N-Benzoyl-2,6-dimethylpiperidine shows a different, interesting special feature: this compound exists in a conformation with *axial* $CH_3$ groups since with the equatorial arrangement there arise unfavourable interactions with the benzoyl group:



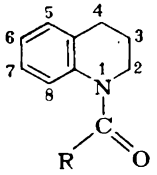
More complex compounds of this type include, in particular, N-acylindoline and N-acyl-1,2,3,4-tetrahydroquinolines. In these compounds, the preferred conformation varies, depending on whether the derivatives of formic or acetic acid are involved. Apart from the Z,E-nomenclature, the conformations of compounds of this type are also designated by the terms *endo* (for the Z-form, the oxygen is directed inside) and *exo* (for the E-form, the oxygen is outside). For example:



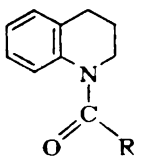

In the equilibrium, there is present 74 per cent of the *exo*-form if R = H and only 11 per cent of the *exo*-form if R = $CH_3$. The *endo*-form is also preferred if R = $C_6H_5$.

The conformations of N-formyl-2-indolinol (XLVI) and N-acetylhexahydrocarbazole (XLVII) have also been studied (67):

With compound XLVII the ratio of the *endo*- and *exo*-forms is 3: 1; the rotational barrier is about 63 kJ/mole. Analogous data have been obtained for N-acyl-1,2,3,4-tetrahydroquinolines (68):



E-Form

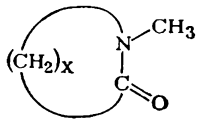


Z-Form

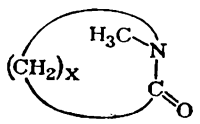
If R = H (a formyl derivative), the E-form predominates almost entirely (about 96 per cent); if R = $CH_3$ (an acetyl derivative), the fraction of this conformation decreases down to 90 per cent. The potential barrier that separates the two conformers is 75 kJ/mole for the formyl derivative and 59 kJ/mole for the acetyl derivative.

When a methoxy group, a bromine atom or a nitro group is introduced into position 6, the population of the Z-conformer appreciably increases. Since it is difficult to visualize any direct steric effect of the substituent situated at C-6, what is meant here is evidently the effect on mesomerism involving the benzene ring and the amide group.

N-Methyl-lactams with a ring containing not more than nine members can exist only in the *cis*-configuration, while for larger rings the existence of *trans*-isomers is also possible (69):



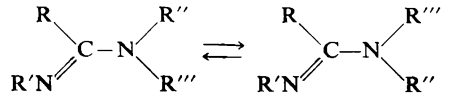
*cis*-Lactam



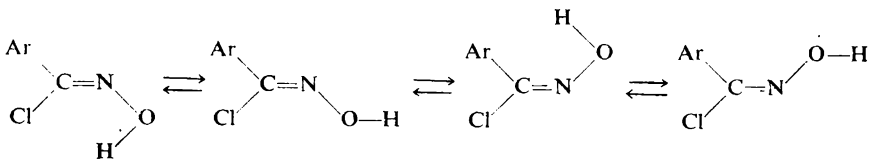
*trans*-Lactam

### 9.7.4. THE ANALOGUES OF AMIDES

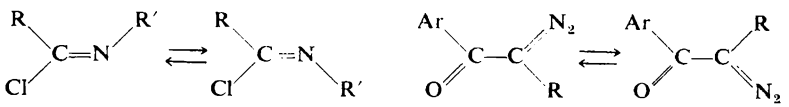
The analogues of amides may be, for example, **amidines**, for which there exists a certain barrier to rotation about the C—N bond (70) (see page 579):



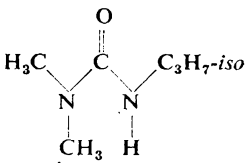
For the acid chlorides of hydroxamic acids, the existence of four stereoisomers can be predicted (71):



In the case of imidoyl chlorides (72) and diazo ketones (73) only two forms can exist:

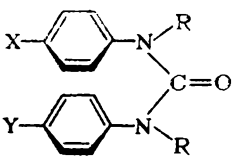


**Substituted ureas** are also the analogues of amides. The conformations of compounds of this type have been studied by using 1,1-dimethyl-3-isopropylurea (74). The preferred conformation of this compound is planar, the barrier to rotation about the CO—N bond being 41 kJ/mole.



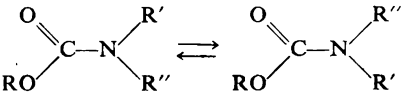
The planar conformation of the ureas is a consequence of the participation in mesomerism of bipolar forms with a double C=N bond, which are similar to the bipolar forms of amides.

Interesting data have been obtained on the conformations of diarylureas (75): these compounds exist in conformations with closely spaced aromatic rings, which, one would think, is extremely unfavourable from steric considerations:

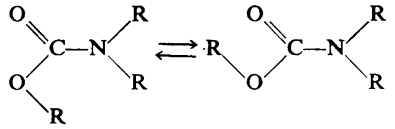


Such a conformation is, however, stabilized by the interaction between the π-electronic systems of the two rings, especially if X is an electron-donating and Y, an electron-accepting substituent. This interaction is compared by the authors with stacking interactions in oligo- and polynucleotides, which lead to the "overlap" of the heterocyclic bases of nucleic acids (see page 627).

For **carbamates**, there can exist two conformers at the partially doubled C—N bond:



Besides, one more problem arises here—the conformation around the C—O bond:



XLVIIIa XLVIIIb

The IR spectral data indicate that conformation XLVIIIa is the preferred one (76). Pure steric considerations do not explain why this is the preferred conformation. It is believed that it is stabilized by the dipole-dipole interaction, whereas conformation XLVIIIb is destabilized by the repulsion of the free electron pairs on nitrogen and oxygen:

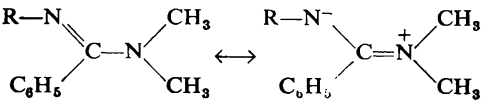
XLVIIIa XLVIIIb

An analogous problem of the conformation about the C—O bond also arises with protonated amides. The proton adds on to the oxygen atom, which leads to the possibility of existence of two conformers:

XLIXa XLIXb

Examination of the NMR spectra shows that conformation XLIXa is the preferred one (77). In connection with the problem of the structure of protonated amides, it should be mentioned that the information reported in the literature on the N-protonation supposedly occurring in dilute acids is refuted by other authors (78).

In the case of substituted **amidines**, just as with amides, the NMR spectra indicate the restricted rotation about the carbon-nitrogen single bond, which results from the active participation of the bipolar form in mesomerism:

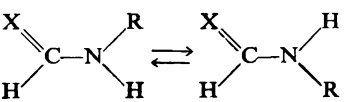


The $CH_3$ groups give two separate signals in the NMR spectra. Two conformers must exist on unsymmetrical substitution.

### 9.7.5. THIOAMIDES AND THEIR ANALOGUES

Much attention is paid to the study of the conformations of sulphur-containing analogues of amides, which are called thioamides. The energy barriers to rotation about the carbon-nitrogen single bond in thioamides are higher than in the corresponding amides (79). It is believed that this is the result of the considerable contribution of the bipolar form (which shortens the C—N distance) and the large atomic radius of sulphur as compared with oxygen. The latter circumstance makes the *cis*-arrangement of the substituent relative to sulphur less favourable than in related oxygen-containing analogues; thus, the fraction of the Z-form in the conformational equilibrium is invariably smaller in thioamides than in the corresponding amides, although the general preference of this form, as a rule, remains valid.

This is seen, for example, from a comparison of formamides and thioformamides:

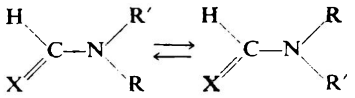


Z-Form E-Form

X = O, S

In the methylamide of formic acid, the fraction of the Z-form is 92 per cent, while that of the thioamide is 88 per cent; the respective figures

for isopropylamide and isopropylthioamide are 84 and 70 per cent and those of *tert*-butylamide and its thio analogue are 70 and 4 per cent, etc. The conformational equilibrium in disubstituted amides and thioamides



La Lb

has been studied and the following data have been obtained (80):

| R | R′ | Content of form La in amides, % | Content of form La in thioamides, % |
|---|---|---|---|
| $CH_3$ | $CH(CH_3)C_6H_5$ | 64 | 73 |
| $CH_3$ | $CH_2C_6H_5$ | 54 | 61 |
| $CH(CH_3)_2$ | $CH_2C_6H_5$ | 30 | 20 |

From these figures it is seen that the increase of the size of the radical situated in the *cis*-position to the sulphur atom (accordingly, to the oxygen atom) has a stronger effect on the conformational equilibrium of thioamides than on that of amides. This is easily explained by the larger size of the sulphur atom as compared with oxygen.

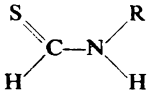
Just as in the case of amides, NMR spectroscopy using shift reagents has proved a promising method for the determination of the configuration of thioamides. The coordination of a lanthanide occurs at the sulphur atom; therefore the signals of the protons of the radical in the *syn*-position to the sulphur atom are shifted more strongly (81).

The barrier separating the Z- and E-conformers of thioamides is substantially higher than in the corresponding amides. This allows one to observe, on a comparatively greater number of cases, the separate existence of conformers as individual stable compounds. This has been done, for example, for nitrogen-disubstituted thioamides of the following structure (82):

R = $CH_3$, $C_2H_5$, *iso*-$C_3H_7$, *tert*-$C_4H_9$

The barrier to rotation about the C—N bond in these compounds is approximately 105 kJ/mole.

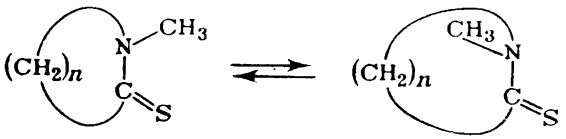
It was shown later (83) that thin-layer chromatography can also be used (at —15°C) to separate the conformers of simpler thioamides—the monoalkylthioamides of formic and acetic acids:



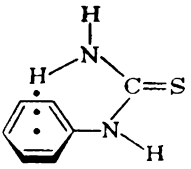
(or $CH_3$)

$R = CH_3,\ CH_2C(CH_3)_3,\ CH_2C_6H_5$

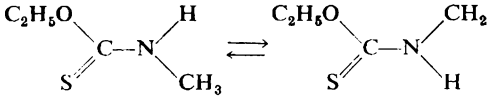
N-Methylthiolactams containing from 5 to 9 members in the ring exist only in the E-form; if the number of members is 12 and larger, the existence of the Z-form becomes possible (84):



**Thioureas** also exist in the Z,E-forms (85). If the substituent at nitrogen is the aryl or benzyl radical, the corresponding thioureas exist exclusively in the E-conformation stabilized by an intramolecular hydrogen bond (86):



According to the NMR spectral data, **thionecarbamates** too exist as an equilibrium mixture of two conformations; for example (87):



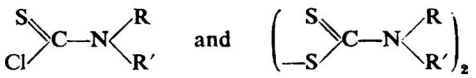
LIa LIb

The percentage content of the conformers in various solvents is as follows:

| Solvent | Content of form LIa, % | Content of form LIb, % |
|---|---|---|
| Carbon tetrachloride | 63 | 37 |
| Pyridine | 76 | 24 |
| Benzene | 67 | 33 |
| Chloroform | 50 | 50 |

Analogous conformers also exist for **thiohydroxamic acids** (88).

The rotational barriers have also been studied for compounds of the type



The magnitude of the barrier expressed in terms of $\Delta G^{\neq}$ is equal to 67-80 kJ/mole. As the size of radicals R and R′ increases the barrier *falls off* somewhat; this evidently results from the destabilization of both the Z- and the E-conformations and of the greater importance acquired under these conditions by non-planar forms (89). The isomerism of compounds of the thioamide type has been studied by Walter (90).

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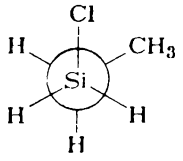
CHAPTER 10

# Stereochemistry of Compounds of Silicon, Phosphorus, Arsenic, Sulphur, Boron, and Other Elements

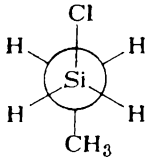
The stereochemistry of compounds, the spatial structure of which follows from the steric features of silicon, phosphorus, arsenic, sulphur, and boron atoms is a rapidly developing field of stereochemistry. A full coverage of this branch of stereochemistry would require the writing of a separate, large book; this chapter is therefore only an introduction to this extensive field.

## 10.1. STEREOCHEMISTRY OF SILICON COMPOUNDS

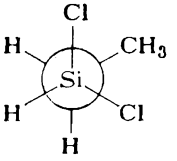
Silicon is the nearest analogue of carbon in the Periodic System of the Elements. Its four-coordinate compounds have the tetrahedral configuration. In studying silanes there arise first of all conformational problems which are quite analogous to those encountered in carbon compounds. As an example may be cited the investigation carried out by Pentin and coworkers (1), which is devoted to the rotational isomerism of ethylmonochlorosilane and ethyldichlorosilane. The molar fractions of the conformers with respect to the carbon-silicon bond in these compounds in the liquid state at 250 K are as follows:



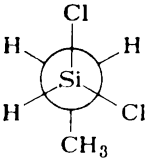

$\varphi^1$ 0.78




$\varphi^3$ 0.22

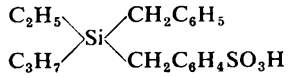



$\varphi^1$ 0.47

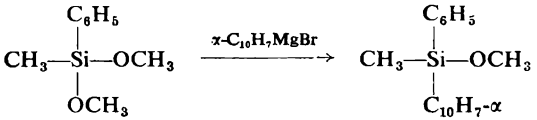



$\varphi^3$ 0.53

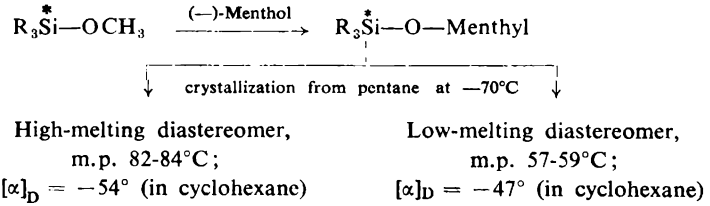
As early as 1910 Kipping showed that the correspondingly built compounds may be optically active due to the asymmetric silicon atom; for example:



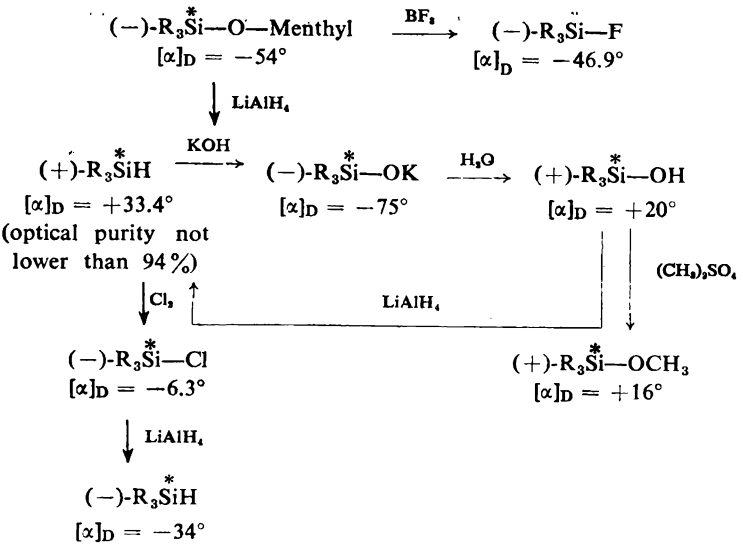
Such compounds drew no special attention: the route to them was too difficult and they themselves did not offer any possibility for further syntheses. A new stage in the investigations of compounds with an asymmetric silicon atom came in 1959 when Sommer and coworkers worked out a convenient method for preparing an optically active silane and discovered a pathway to a large number of its conversion products. The starting material was methylphenyldimethoxysilane, which was converted by the action of α-naphthylmagnesium bromide into methylphenylnaphthylmethoxysilane:



This compound with an asymmetric silicon atom was resolved by Sommer into optical antipodes (enantiomers) through its conversion with the aid of menthol into a diastereomeric pair; the diastereomers were then separated by means of low-temperature recrystallization from pentane. In the schemes given below, the organosilicon radical $(CH_3)C_6H_5(\alpha\text{-}C_{10}H_7)Si$ will be denoted as $R_3\overset{\bullet}{Si}$.

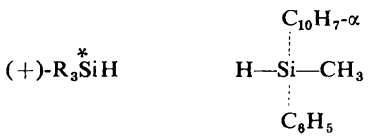


The diastereomers were used as the starting compounds for preparing optically active silanes $R_3Si^*H$ and many other compounds.




Owing to these and many other reactions, methylphenylnaphthylsilane became the parent of more than a hundred of optically active organosilicon compounds. In a short period there was developed an entirely new branch of stereochemistry—the stereochemistry of silicon compounds, and the mechanisms of substitution reactions at the silicon atom were studied. In the 1965's Sommer was able to sum up his investigations in this field (2, 3).

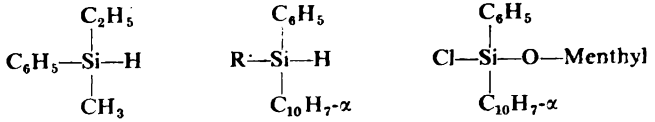
The X-ray structure analysis was used to determine the absolute configuration of the starting silane:




The configurations of other compounds were established by using the method of quasi-racemates and ORD curves. A knowledge of the configuration enabled establishing in which reactions the configuration is retained and in which the inversion of configuration is involved. The outcome was the development of the conception of three principal mechanisms of substitution reactions at the asymmetric silicon atom:

(1) $S_N1$-Si, accompanied by racemization;
(2) $S_N2$-Si, involving inversion of configuration;
(3) $S_Ni$-Si, involving retention of configuration.

Later, there were synthesized optically active silanes containing other radicals (4):

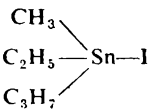


The investigation of optically active silicon compounds is carried on at present by various authors (5).

The method used by Sommer for preparing an optically active silane has been successfully employed for preparing an analogous compound with an asymmetric germanium atom.

The configuration was determined by means of the method of quasi-racemates; the reference standard used was the corresponding silane. A knowledge of the configuration made it possible to undertake an investigation into the stereochemistry of substitution reactions at the germanium asymmetric centre (6).

As early as the beginning of this century Pope showed that a compound with an asymmetric tin atom could be obtained in an optically active form.



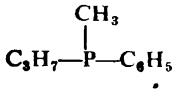
This compound appeared to be readily racemizable.

## 10.2. STEREOCHEMISTRY OF PHOSPHORUS COMPOUNDS

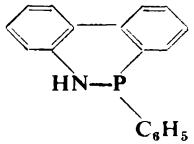
For the nitrogen analogues in the Periodic System—phosphorus, arsenic, antimony—the stability of the pyramidal configuration increases with increasing atomic weight. The calculations made on the basis of the observed frequencies in the vibrational spectra gave the following values for the frequency of inversion of the pyramid (and, hence, for

the lifetime of the optically active molecule): $NH_3$, $2.5 \times 10^{-11}$ sec; $PH_3$, $2.3 \times 10^{-6}$ sec; $(CH_3)_3P$, 2 hours; $AsH_3$, 1.4 years.

Experimental data also support the greater stability of the configuration of phosphorus derivatives than that of those of nitrogen. For example, methylpropylphenylphosphine I was obtained in an optically active form. It is racemized but slowly in boiling toluene; the activation energy of the racemization reaction is about 100 kJ/mole. Another example of an optically active compound with trivalent phosphorus is compound II.



I



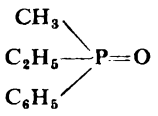
II

A review article has been published on the preparation of optically active tertiary phosphines and their properties (7).

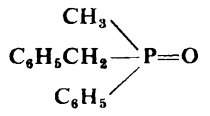
The barrier to pyramidal inversion for methylphenyl-*tert*-butylphosphine is equal to 134 kJ/mole (8) but if phosphorus is linked to an atom capable of ($p$—$d$)-$\pi$ conjugation (e.g., silicon), the barrier falls off (9).

The conformations of phosphines have been studied little. The barrier to rotation about the C—P bond in *tert*-butylphosphine dichloride, $(CH_3)_3C—PCl_2$, is 27 kJ/mole at 160 K instead of 46 kJ/mole for the carbon analogue (2,2-dichloro-3,3-dimethylbutane). This is accounted for (10) by the greater C—P bond length as compared with the C—C bond.

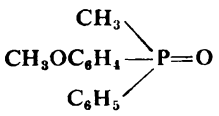
The various compounds of four-coordinate phosphorus, which possess tetrahedral symmetry, have been produced in optically active forms. Among these compounds are phosphine oxides (11), e.g., III-VI; the derivatives of phosphinic and thiophosphinic acids (12), e.g., VII-IX, phosphonium salts (13).



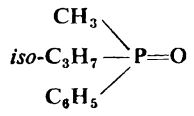
III



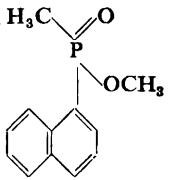
IV



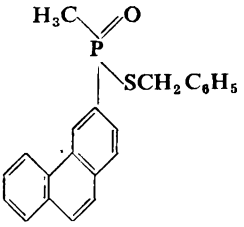
V



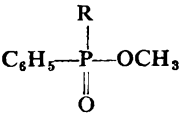
VI



VII

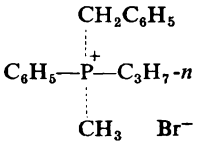


VIII



IX

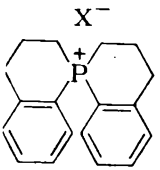
The absolute configuration of benzylmethylphenyl-*n*-propylphosphonium bromide has been determined by means of X-ray diffraction analysis (14); it corresponds to formula X for the dextrorotatory isomer:



X

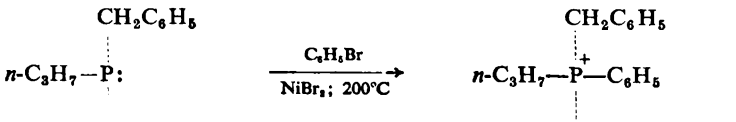
(+)-

The possibility of creation of molecular asymmetry of the spiran type with phosphorus as the junction atom has been demonstrated through the use of compound XI:



XI

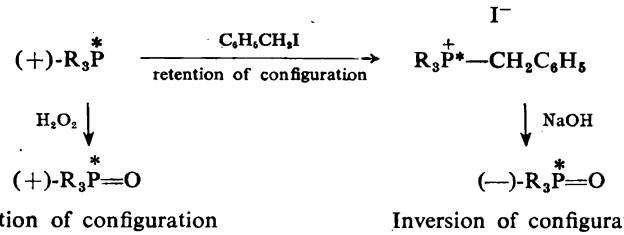
The preparation of optically active compounds with an asymmetric phosphorus atom has made it possible to study the stereochemistry of reactions affecting a chiral centre of this type (see ref. 15 for a review article). The reactions of addition across the free electron pair of tertiary phosphines proceed with retention of configuration. They include conversions into phosphine oxides, quaternary phosphonium bases; for example (16):



(−)-Methylpropylbenzylphosphine

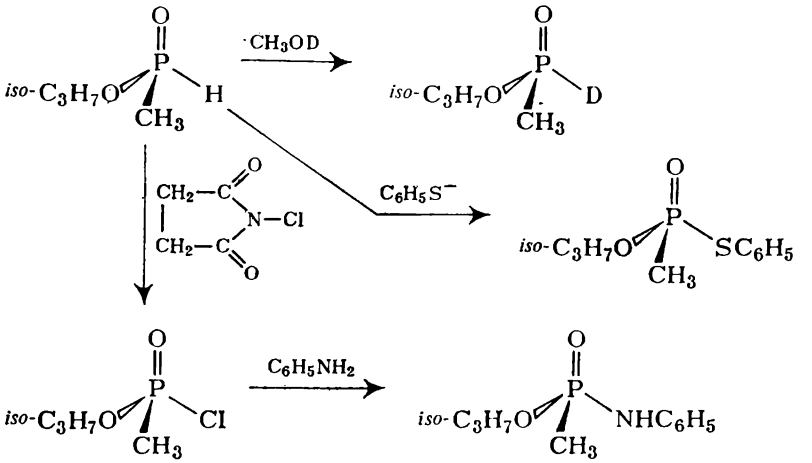
*S*-(+)-Methylpropylbenzylphosphonium bromide

(+)-Methylpropylphenylphosphine (designated as $R_3P^*$ further in the text) can be converted into the corresponding oxide by two routes, the stereochemical results being different:

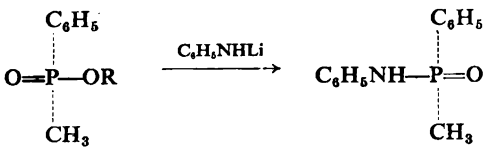



Thus, reactions that affect the chiral phosphorus atom may proceed, like the corresponding reactions at the carbon atom, both with retention and inversion of configuration.

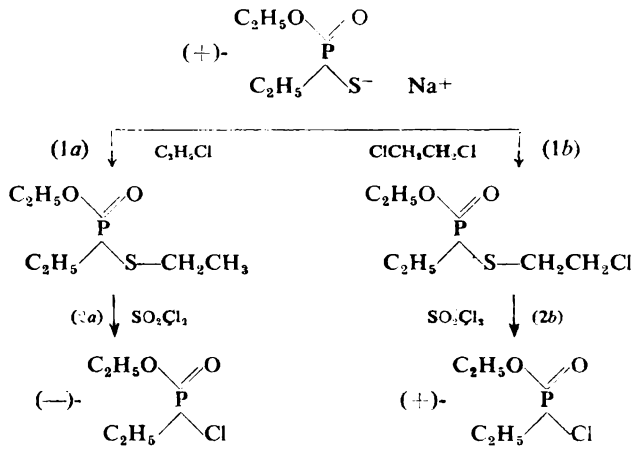
A study of the stereochemistry of reactions of substitution of hydrogen in (—)-isopropylmethyl phosphinate (17) has shown that these reactions take place with retention of configuration at the phosphorus atom:




The replacement of the OR residue by NHR in optically active esters of phosphinic acids occurs with inversion of configuration (18):

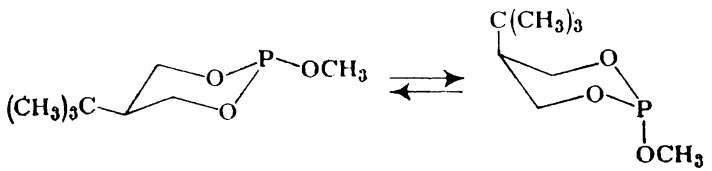


The stereochemical result of substitution reactions at the phosphorus atom may vary even with small changes in the structure of the reacting substances. This is clearly demonstrated by the example given below, where two compounds, which differ only in that one has the $-SCH_2CH_3$ grouping and the other, the $-SCH_2CH_2Cl$ grouping, give different stereochemical results upon substitution of chlorine for a sulphur-containing group according to the scheme:




In reactions (1*a*) and (1*b*), the steric centre remains untouched; the compounds resulting from these reactions have the same configuration corresponding to the configuration of the starting compound. If, however, they are reacted with the same reagent, sulphuryl chloride, the stereochemical results are diametrically opposite!

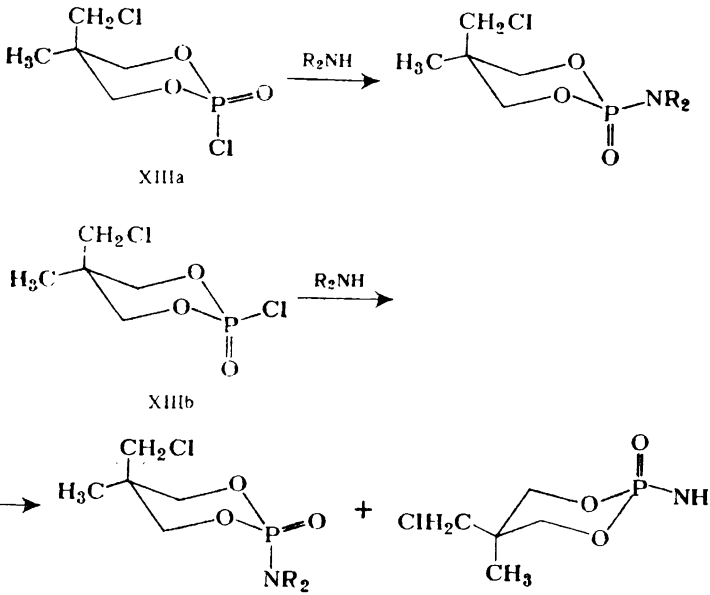
In 1970, there was published a work (19) which initiated the study of the conformations of six-membered phosphorus-containing heterocyclic compounds. As the simplest model, there were taken cyclic phosphites, for which two chair conformations can be predicted:



XIIa XIIb

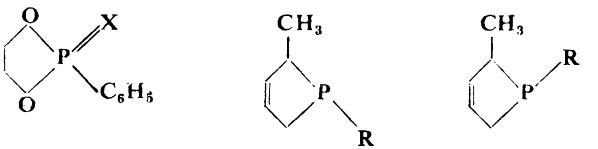
By analogy with cyclohexane, there could have been expected the prevalence of the diequatorial form XIIa, but the investigation carried

out by means of NMR spectroscopy showed that the form XIIb predominates in the conformational equilibrium. This is evidently the result of a dipole-dipole repulsion closely related to the anomeric effect in the series of tetrahydropyrans (see page 526). The stereochemistry of reactions of compounds of this type has also been studied; for example, the action of piperidine on the stereoisomeric compounds XIIIa and XIIIb has been examined (20):



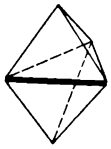

The replacement of chlorine by the amino group proceeds with inversion of configuration at the phosphorus atom. It is interesting that the reaction product of compound XIIIb exists as two quite stable conformers which are not liable to undergo interconversion even at 250°C.

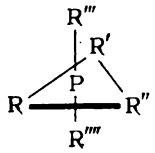
Other phosphorus-containing heterocyclic systems are also known; for example (21):

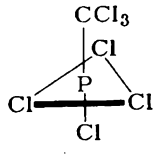



The last two compounds are *cis-trans* isomers which were separated by means of gas-liquid chromatography.

Wittig showed that phosphorus, in contrast to nitrogen, can form five true covalent bonds due to the extension of the octet. In such compounds, phosphorus has the configuration of a trigonal bipyramid:






XIV

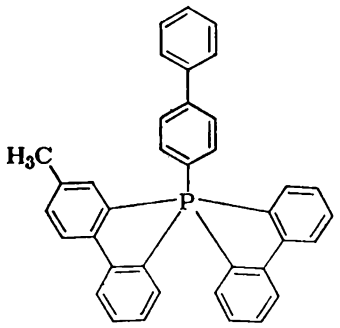
The five substituents occupy stereochemically different positions: three of them (R, R′, R″) lie in the same plane with the phosphorus atom (equatorial substituents), and the other two (R‴, R⁗), above and below this plane (apical substituents). One example is compound XIV in which the trichloromethyl group occupies the apical position (22).

Phosphoranes P(RR′R″R‴R⁗) in which all the five substituents are different may, in principle, exist in the form of 20 chiral isomers making up 10 pairs of optical antipodes (enantiomers). If two substituents are identical, the number of isomers reduces to 10, including two pairs of optical antipodes.

Although the conventional representations may lead one to think that the apical substituents are arranged more "freely", this is not the case in reality: the apical substituent interacts sterically with three equatorial substituents situated at an angle of 90° to it, whereas the equatorial substituents are far apart from one another at angles of 120°.

Structures with five-coordinate phosphorus are of greater importance as intermediates in reactions of compounds of four-coordinate phosphorus, such as phosphonium salts, phosphine oxides, esters of phosphinic, phosphonic and phosphoric acids (phosphinates, phosphonates, phosphorates). The stereochemical characteristics of the reactions of these compounds can be understood if one takes into account the special features of the transiently formed compounds of five-coordinate phosphorus, namely: substituents readily enter the apical positions and are readily eliminated from them; the predominantly equatorial position of $O^-$ with the possible apical or equatorial position of the hydroxyl group; the exclusively apical-equatorial incorporation of five-coordinate phosphorus into four- and five-membered rings; the preferable diequatorial insertion into six-membered rings; the possible isomerization with migration from the apical to the equatorial position and vice versa.

Pentaphenylphosphoranes have also been produced in optically active forms (23); an example is compound XV:



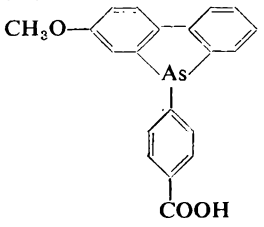

XV

$[M]_{578}^{24} = 472 \pm 5°$

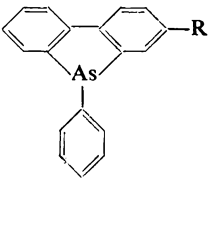
The spatial structure of compound XV differs greatly from the structure of ordinary phosphoranes: it has the form of a strongly distorted tetragonal pyramid.

## 10.3. STEREOCHEMISTRY OF ARSENIC COMPOUNDS

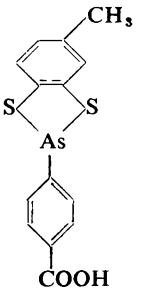
There have been studied optically active compounds with three- and four-coordinate arsenic atom as the chiral centre. Among them are compounds in which the arsenic atom is contained in the ring (24) and simpler arsines (25):



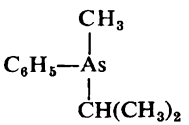

XVI




XVII



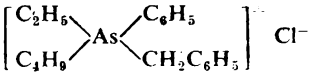

XVIII




XIX

The barrier to pyramidal inversion in compound XIX is 173 kJ/mole, i.e., racemization proceeds with difficulty. If the arsenic atom carries atoms such as silicon, germanium, tin, the inversion barrier decreases down to 75-105 kJ/mole.

Optically active arsonium salts have also been described, for example, ethylbutylphenylbenzylarsonium chloride

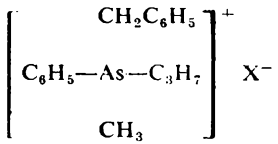


One curious misconception is associated with this compound.

The first publication on the optical activity of this compound is due to Kamai (26). In this publication, the compound was described as readily racemizable, whereas Horner (27), who obtained this compound at a later time, observed no racemization. It turned out that actually the compound that Kamai had at his disposal was not in an optically active form. Kamai passed the racemate of this compound through a column with optically active quartz in the hope that, as a result of asymmetric adsorption (see page 149), there would appear optical activity. And indeed the solution passed through the column was optically active but this activity disappeared after a short time, i.e., racemization apparently occurred.

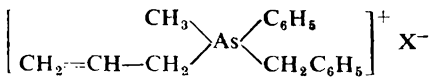
The true explanation for the observed facts, as was established by Horner and Hofer when they repeated the Kamai experiments, was however quite different. To increase the adsorbing power of quartz, Kamai placed finely ground quartz in the column. When the solution was passed through the column, the tiny particles of quartz were washed off, forming a suspension. It was these particles that gave optical rotation in measurements: they then gradually settled down, thus imitating racemization.

The absolute configuration has been determined for a number of arsonium salts, for example (28):



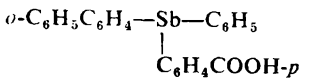
Levorotatory antipode (R-configuration)

Having studied a series of reactions of an optically active arsonium salt of the structure



Horner (29) showed that the hydrogenation of this compound and the subsequent removal of the benzyl group with the aid of the so-called cathodic resolution, i.e., the transformation into the tertiary arsine $C_6H_5As(CH_3)(C_3H_7)$, and also the reverse reaction proceeded with retention of configuration at the arsenic atom.

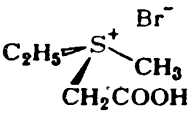
Recall that optically active compounds of trivalent antimony are also known. Thus, Campbell (30) resolved the following compound into enantiomers by means of α-phenylethylamine:



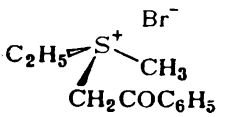
XX

## 10.4. STEREOCHEMISTRY OF SULPHUR COMPOUNDS

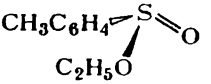
Compounds with three-coordinate sulphur have the pyramidal configuration, like compounds of trivalent nitrogen, phosphorus, and arsenic. The fundamental difference is that the sulphur pyramid is very stable and incapable of inversion, as is observed, for example, in the case of nitrogen. Examples of compounds of this type are sulphonium salts (e.g., XXI, XXII), sulphinic acids and their derivatives (e.g., XXIII), sulphoxides; the last-named compounds have been studied the most thoroughly.



XXI



XXII

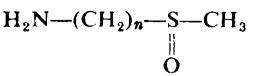


XXIII

In their chemical constitution sulphoxides are analogous to ketones:

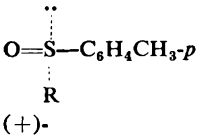
The spatial structures of these two classes of compounds are however different. The $sp^2$-hybridization of the carbon atom in ketones renders the entire grouping planar and therefore excludes the possibility of asymmetry. In sulphoxides, as has already been mentioned, the sulphur atom is at the summit of a stable pyramid.

In 1950, Karrer described a series of optically active aliphatic sulphoxides



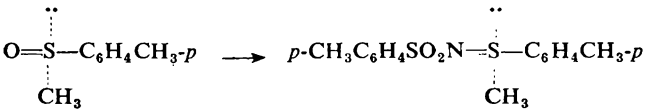
which contain an extra amino group (and which are therefore convenient for being resolved with the aid of acidic asymmetric reagents). Numerous determinations of the configuration of sulphoxides were made in the 1960's (31). The various methods were used in these determinations: chemical correlation, comparison of ORD and CD data, stereospecific

asymmetric synthesis, NMR spectra in chiral solvents. As a result of these determinations, there were established the configurations, say, of the following compounds possessing positive rotation:

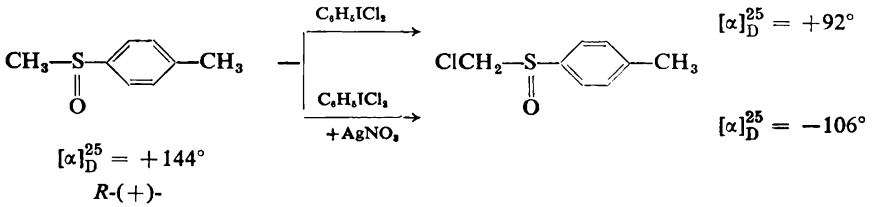



R=$CH_3$, $C_4H_9$, $CH_2C_6H_5$

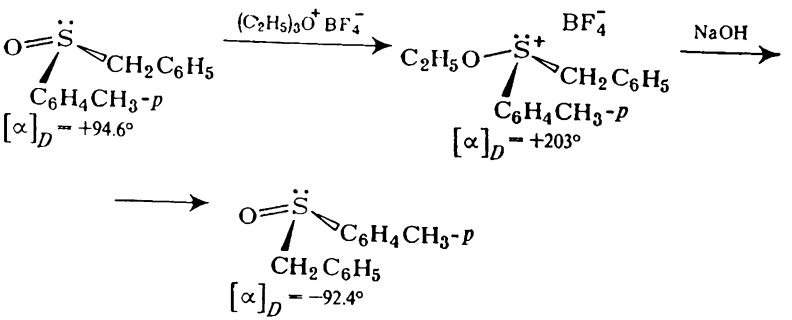
The data obtained on the configurations were used as the starting point for works on the stereochemistry of the reactions of sulphoxides. It has been shown, for example, that methyl-*p*-tolylsulphoxide retains its configuration upon replacement of oxygen by nitrogen-containing residues (32); for example:



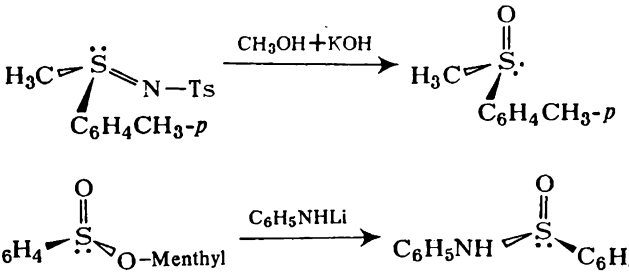

The reaction of methyl-*p*-tolylsulphoxide with chlorinating reagents may however proceed, depending on the conditions used, either with retention or with inversion of configuration, although formally the chiral centre remains unaffected in the reaction (33):



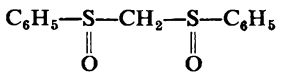

The conversion of benzyl-*p*-tolylsulphoxide given below is accompanied by inversion of configuration (34):



The inversion of configuration has also been observed in the following reactions of substitution at the asymmetric sulphur atom (18):




Compounds with two sulphoxide chiral centres exist in diastereomeric forms (35); for example:

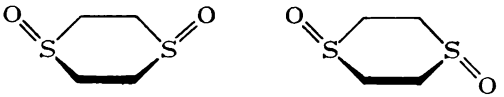



*meso*-form, m.p. 118-120°C

racemate, m.p. 182-183°C

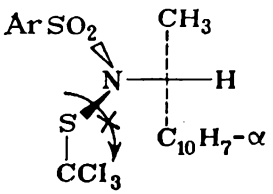
The diastereomers can be separated by crystallization from acetone.

The isomerism of cyclic compounds containing two sulphoxide groups in the ring is similar to the stereoisomerism of alicyclic compounds with two substituents. Such compounds exist in *cis-trans* forms:

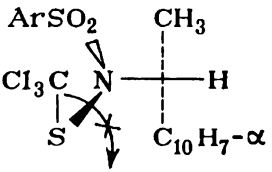


*cis*-Form *trans*-Form

Compound XXIV which belong to the class of sulphenamides forms two diastereomers:



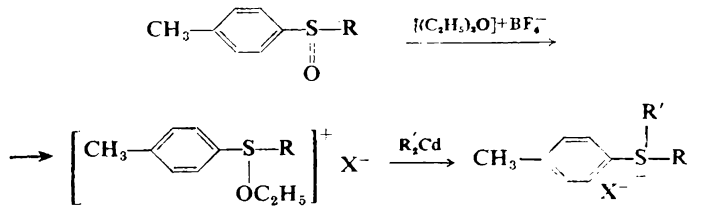

XXIVa



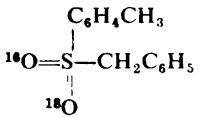

XXIVb

One element of chirality here is the residue of optically active α-naphthylethylamine possessing usual carbon asymmetry. A second element of chirality arises as the result of restricted rotation about the S—N axis of chirality; the rotational barrier is about 80 kJ/mole (36).

Optically active **sulphonium salts** can be produced from sulphoxides according to the scheme:

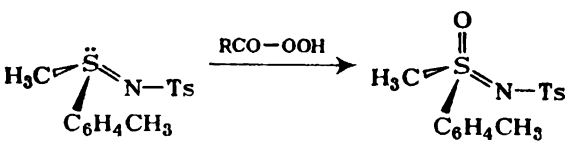


Four-coordinate sulphur is contained in sulphones, R—$SO_2$—R. One would think that the creation of asymmetry is impossible in this case since the two substituents in the sulphone tetrahedron are identical (oxygen atoms). Nevertheless, optically active compounds of this type have been obtained due to the **isotope asymmetry** (38):



$[\alpha]_D = -0.16 \pm 0.05°$

The studies carried out by Cram (39) have shown that on conversion of the three-coordinate chiral sulphur atom into a four-coordinate one the configuration is retained—the reaction occurs at the free electron pair, the bonds present remaining unaffected:

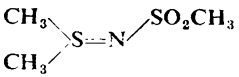


**Sulphines**, i.e., compounds containing the grouping $\diagdown C{=}S{=}O$, belong to the category of heterocumulene systems. However, whereas in the simplest cumulenes (allenes) the linear arrangement of C=C=C creates conditions for the appearance of chirality, in sulphines the cumu-

lene system has an *angular* structure, which allows for geometrical isomerism; for example:

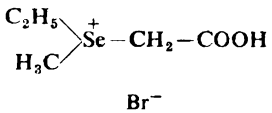
The configuration of the isomers was determined by means of NMR spectroscopy, using shift reagents (40); the oxygen-coordinating reagent causes a stronger shift of the proton signals of the aromatic substituent that occupies the *cis*-position relative to oxygen.

Compounds with the S=N double bond are also known to exist; one example is (41):



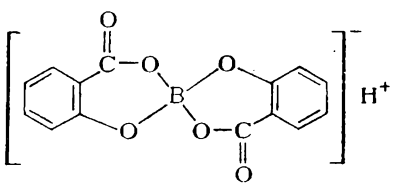
If the sulphur atom bears two different radicals, such compounds must exist in geometrically isomeric forms.

There are also known optically active compounds with asymmetric atoms of other elements of Group VI of the Periodic System—selenium, tellurium (42); for example:

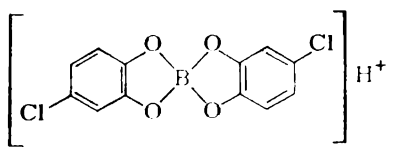


## 10.5. STEREOCHEMISTRY OF BORON COMPOUNDS

Boron, which is three-coordinate in its ordinary compounds, may be four-coordinate in complexes. The optical activity of compounds of this type has been detected by Böeseken in 1924 for borosalicylic acid XXV:



XXV



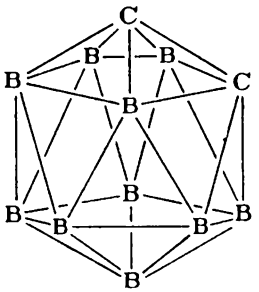
XXVI

The acid XXV in its optically active form has not yet been isolated; the existence of optical isomers was deduced only from the fact that the fractional crystallization of quinic acid gave fractions possessing right-handed rotation, whereas quinine and its salt formed with salicylic acid rotated to the left.

The same author made an attempt in 1925 to prepare, in an optically active form, another boron-containing complex, bis-(4-chloropyrocatechol)-boric acid XXVI. The compound itself could not be isolated in an optically active form, but the partial resolution and the rapid racemization involved could be judged by the observed mutarotation of the alkaloid salts.

The first of these compounds gave rise to a curious dispute. When Böeseken published his work on optically active borosalicylic acid, Rosenheim declared that he could not imagine where the optical activity had come from. Immediately after this statement, Rosenheim received a number of letters in which he was reminded of the existence of asymmetry in spirans, and so in the next issue of the journal Rosenheim had to apologize (43).

Interesting stereochemical characteristics are displayed by **carboranes,** which are bulky polyhedral structures produced from boron hydrides and acetylene. The most thoroughly studied of them is decacarborane which has the composition $B_{10}C_2H_{12}$. The compound has the structure of a polygonal dodecahedron with carbon and boron at the apexes.




Each of the atoms shown has one more hydrogen atom (not shown in the formula). Both the boron and the carbon are in unusual valence states in carboranes—they are formally hexavalent. If the carbon atoms are next to each other (orthocarboranes) or separated by one boron atom (metacarboranes), the entire figure acquires asymmetry and is therefore capable of existence in optically active forms.

The optical activity caused by non-carbon asymmetric centres has been examined by Sokolov and Reutov (44).

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CHAPTER 11

# Stereochemistry of Natural Compounds

The spatial structure has a decisive influence on the properties and biological functions of organic compounds that participate in the life processes. The majority of such compounds are optically active and are encountered in nature in one of the antipode forms: this refers to proteins and the protein-forming amino acids, nucleic acids, sugars, steroidal hormones, naturally occurring hydroxy acids, enzymes, vitamins, etc. The properties of natural rubber are intimately associated with the definite geometrical configuration of its polymeric chain. Of greater importance in this field is the **conformation,** especially if polymers, such as proteins and nucleic acids, are concerned. None of the problems of biochemistry can be solved on the present-day level without a thorough consideration of stereochemical factors.

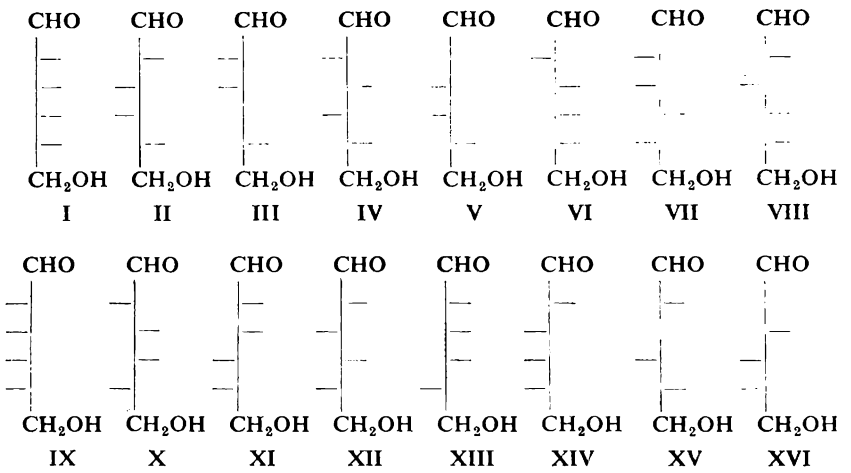
A detailed treatment of the stereochemistry of natural compounds would require a book several times exceeding in size the present book. Therefore, the content of this chapter should be regarded only as an introduction to the extensive branch of the stereochemistry of natural compounds.

## 11.1. CARBOHYDRATES

### 11.1.1. DETERMINATION OF THE CONFIGURATION OF MONOSACCHARIDES

The configuration of monosaccharides was the subject of the classical works of Emil Fischer. Let us consider the course of the determination

of the configuration of sugars in the same manner as was done in the early 1890's by E. Fischer. We shall only replace the designations of the configurations of asymmetric centres [with the aid of the signs (+) and (—)] used by Fischer with projection formulas and also change somewhat the construction of the general table of the configurations of sugars. In his reasoning E. Fischer used the table of sixteen possible spatial configurations of aldohexoses I-XVI which he borrowed from the book written by van't Hoff (in the conventional formulas given below the horizontal lines indicate the position of the hydroxyl group in projection formulas):


CHO CHO CHO CHO CHO CHO CHO CHO
CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH
I II III IV V VI VII VIII
CHO CHO CHO CHO CHO CHO CHO CHO
CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH CH2OH
IX X XI XII XIII XIV XV XVI

The first task facing Fischer was to decide which of these sixteen formulas could be assigned to dextrorotatory glucose, which is the most important and the most widespread monosaccharide. The solution of this problem was based on the logical analysis of the following experimental facts.

1. On oxidation dextrorotatory glucose gives an *optically active* dibasic acid (saccharic acid); this permits rejecting formulas I and II (and the corresponding antipode formulas IX and X) since from sugars of this structure there are formed *meso-forms* of dicarboxylic acids.

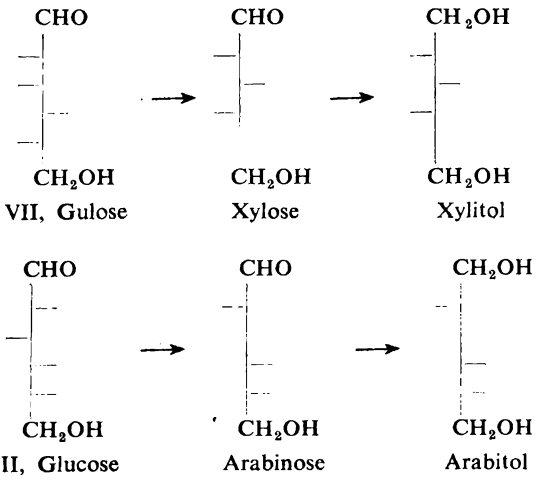
2. Optically active saccharic acid can be produced by oxidation not only of glucose but also of another monosaccharide, gulose. This means that glucose and gulose differ from each other only by the disposition of the CHO and $CH_2OH$ groups; these sugars cannot thus be represented by formulas III and IV (and by their antipodes XI and XII): the interchange of the CHO and $CH_2OH$ groups in these formulas leads not to a new projection formula but to the starting one!

3. Mannose forms the same osazone as glucose: this means that both sugars are **epimeric**, i.e., differ only in the configuration of the asymmetric centre closest to the aldehyde group. Mannose, like glucose, forms on oxidation an optically active dibasic acid (mannosaccharic acid) *different* from that formed by glucose.

Suppose that glucose has formula V (or XIII); we are now to check up whether the facts presented in 3 could be reconciled with this formula. If formula V represents glucose, then its epimer, mannose, must have formula II. The sugar represented by formula II on oxidation can yield only the *meso-form* of a dibasic acid: this is not in accord with what is known of mannose and, hence, formula V (or XIII) must be dispensed with. A quite analogous reasoning shows that glucose cannot have formulas VI (or XIV).

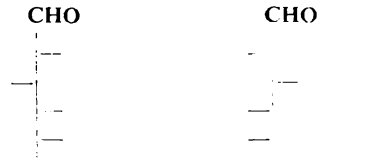
There remain two possible formulas, VII and VIII (and their antipodes XV and XVI).

4. When subjected to degradation with removal of the asymmetric centre adjacent to the aldehyde group, glucose is converted into a pentose (arabinose), which on reduction gives an *optically active* pentahydric alcohol (arabitol). On degradation followed by reduction gulose yields an optically inactive alcohol (xylitol) which is a *meso*-form. These transformations may be described by the following short-hand notation (it is given for one pair, VII and VIII; it may accordingly be written for the pair XV and XVI):




Glucose exists however in the form of a pair of antipodes: dextrorotatory and levorotatory glucoses. Which of the projection formulas, VIII or XVI, corresponds to dextrorotatory glucose and which, to levorota-

tory glucose? Fischer could not provide an answer to this question and he therefore postulated that dextrorotatory glucose should be represented by formula VIII, and levorotatory glucose by formula XVI:




(+)-Glucose VIII (−)-Glucose XVI

In subsequent years, after the absolute configurations had been established, it turned out that the arbitrary choice made by E. Fischer was *correct.*

Based on the adopted configuration of glucose, without making resort to new experimental facts, formula VII was assigned to gulose and formula III to mannose:

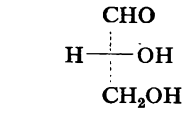
VII, (+)-Gulose III, (+)-Mannose

Since it is known that (+)-glucose can be converted into natural fructose which rotates to the left, its configurational formula may also be written:

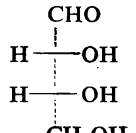
VIII, (+)-Glucose (−)-Fructose

The configurations of other hexoses have been elucidated in an analogous manner. Without considering the details of the route used for the

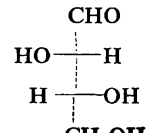
purpose, we shall present the configurations of monosaccharides of the D series in the form of a single scheme:



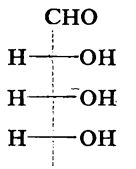

D-(+)-Glyceraldehyde



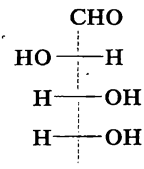

(−)-Erythrose



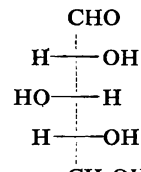

(−)-Threose



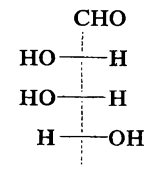

(−)-Ribose



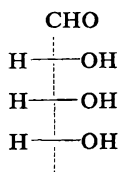

(−)-Arabinose



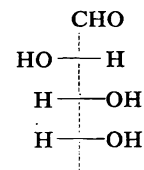

(+)-Xylose



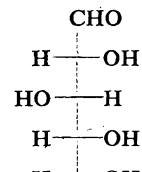

(−)-Lyxose



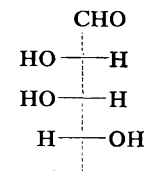

(+)-Allose



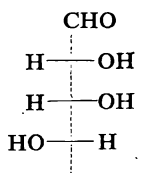

(+)-Altrose



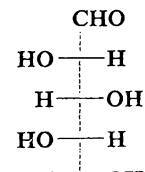

(+)-Glucose



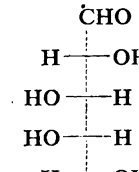

(+)-Mannose



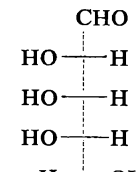

(−)-Gulose




(−)-Idose




(+)-Galactose



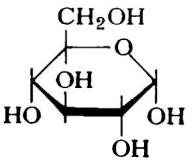

(+)-Talose

Almost exclusively monosaccharides of the D-series occur in nature, but exceptions are also known. For example, L-arabinose is found in the form of glucosides in plants of the aloe family.

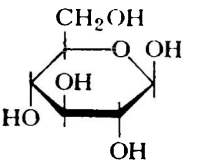
The elucidation of the configurations of the aldehyde forms of carbohydrates does not yet provide the complete detailed picture of the spatial structure of these compounds. Two forms (α- and β-) of dextrorotatory glucose are in fact known to exist:

| | | Glucose | Methylglucoside |
|---|---|---|---|
| M.p., °C | α-form | 146 | 168 |
| | β-form | 148-150 | 104 |
| $[\alpha]_D$ | α-form | +110 | +157 |
| | β-form | +19.3 | −33 |

These isomers are represented by cyclic formulas which differ in the spatial arrangement of the glucosidic hydroxyl group, i.e., in the configuration of an additional asymmetric centre which arises upon transformation into a cyclic form:




α-D-Glucose




β-D-Glucose

In aqueous solution there gradually sets in an equilibrium between the two forms. An external manifestation of this is the phenomenon of mutarotation—a gradual decrease of the specific rotation of freshly prepared solutions of glucose from $[\alpha]_D = +110$ to $+52°$ (the latter is the rotation of the equilibrium mixture of the α- and β-forms of glucose in water). When crystalline glucose is precipitated from an equilibrium aqueous solution, it is again separated entirely in the α-form. Pure β-glucose can be obtained by crystallization from pyridine.

In passing from the aldehyde formula of glucose to the cyclic formula there arise a number of problems that require solution: the fact of for-

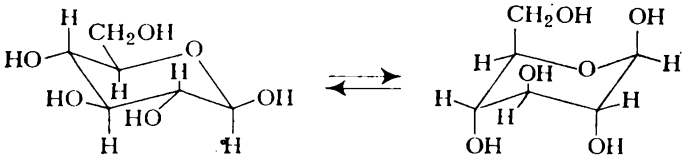
mation of a *six-membered* ring must be proved; it is necessary to prove the configuration of the glucoside asymmetric centre. (For a treatment of these problems, see ref. 1.) We shall only note that the formulas of α- and β-glucose given above do not provide a complete idea of its spatial structure: the ring is in fact non-planar and has the chair form as is the case with cyclohexane.

### 11.1.2. CONFORMATIONS OF SUGARS

The **conformations** of sugars have been studied at present; we shall primarily be concerned with the conformations of monosaccharides.

It should be mentioned that the term "conformation" appeared for the first time in connection with the discussion of the spatial structure of sugars. A review article devoted to the conformations of sugars is available in the literature (2); an extensive material on the subject is also given by Eliel in his book (3).

For the series of D-aldopyranoses there are usually considered two conformations which are shown below for glucose and which are capable of interconversion (like the two conformations of the cyclohexane chair):



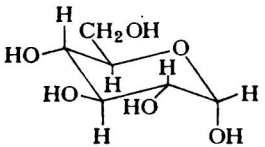

β-D-Glucose in conformation *C*1 ⇌ β-D-Glucose in conformation 1*C*

Conformation *C*1 (normal) for glucose has a substantial advantage over conformation 1*C* (alternative) since in the first conformation all the hydroxyl groups are equatorial, and in the second, they are axial. In the case of other monosaccharides, the difference in stability between the conformations *C*1 and 1*C* may not be so great, and for α-D-arabinose the conformation 1*C* is even more stable.

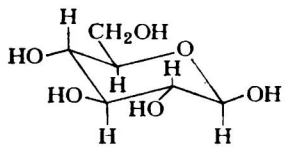
Having the normal conformation with all the hydroxyl groups being equatorial, glucose is thermodynamically the most stable monosaccharide. It is not surprising that it is glucose that plays such an important role in nature. The interaction energies, calculated by Reeves (4), which increase the conformational energy and lower the stability, have the following values; they are associated with the position of the equilibrium of the α,β-anomeric forms:

| Monosaccharide | Free energy of the α-form, kJ/mole | Free energy of the β-form, kJ/mole | Fraction of the α-form in equilibrium (PMR), % |
|---|---|---|---|
| Glucose | 10.1 | 8.6 | 36 |
| Mannose | 10.5 | 12.4 | 67 |
| Galactose | 11.9 | 10.5 | 27 |
| Talose | 14.8 | 16.8 | 58 |
| Allose | 16.1 | 12.4 | 20 |
| Gulose | 3.85 | 3.05 | 22 |
| Xylose | 1.9 | 1.6 | 33 |
| Lyxose | 1.85 | 2.4 | 71 |
| Arabinose | 1.95 | 2.2 | 63 |
| Rybose | 3.1 | 2.3 | 26 |

The prevalence of the β-isomer in the equilibrium in the case of glucose is understandable from the conformational viewpoint since this anomer contains an equatorial glycosidic hydroxyl group:



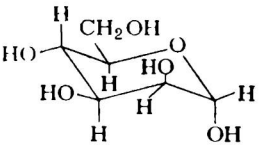
α-Glucose, 37%



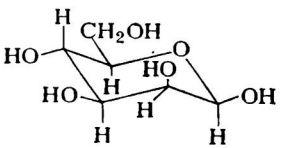
β-Glucose, 63%

The existence of a certain fraction of α-glucose, which is a sterically unfavourable anomer with an axial hydroxyl group, is a consequence of the manifestation of the anomeric effect. This effect, as has already been said (see page 527), is a result of a dipole-dipole repulsion: it is weakened in aqueous solutions because of the high dielectric constant of water. The anomeric effect should be expected to be more pronounced in solvents of lower dielectric constant and the fraction of α-glucose should be expected to increase. Indeed, in methanol it amounts to 50 per cent.

The thermodynamic stability of mannose is somewhat lower than the stability of glucose since one of the hydroxyl groups in mannose is axial:



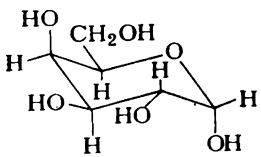
α-Mannose, 69%



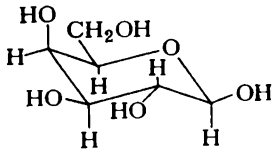
β-Mannose, 31%

In the equilibrium of the anomeric forms there predominates α-mannose with the *axial* orientation of the glycosidic hydroxyl group; this is also a manifestation of the anomeric effect—the stabilization of the axial orientation under the influence of the adjacent pyran oxygen. In a medium of lower dielectric constant (in pyridine) the fraction of α-mannose increases up to 85 per cent.

The stability of galactose is also lower than that of glucose: it has an axial hydroxyl group at C-4:




α-Galactose, 30%

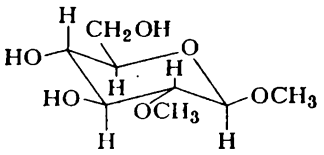



β-Galactose, 70%

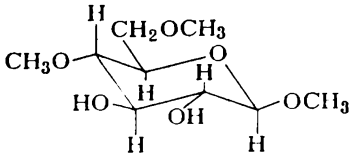
An important part in the investigation of the conformation of carbohydrates has been played by a copper-ammonium complex (cuprammonium). The complex formation involves the $Cu(NH_3)_4^{2+}$ ion which interacts with two hydroxyl groups (more often, those on adjacent carbon atoms). For a complex to be formed, it is necessary that the dihedral angle between the two OH groups be small: the reaction proceeds well with a dihedral angle of 60° and does not take place at 120 and 180° (this is shown on the models with a rigid conformation).

Complex formation is detected by a decrease in the electrical conductivity of the solution (i.e., by an increase of its electrical resistivity) and also by a change in the optical rotation. Both these signs may vary, independently of each other. Optical rotation is strongly changed only when a complex is formed with the dihedral angle between the OH groups being about 60°: in this case the complex formation distorts the ring, which is what leads to the change of optical rotation. Such an angle is present when the complex formation involves the adjacent OH groups having the *e,e*- or *a,e*-conformation. If, however, the OH groups in the starting monosaccharide occupy only the *cis*- (the dihedral angle is equal to zero) or the 1,3-diaxial positions, then complexing does not change the conformation of the molecule; accordingly, the optical rotation is slightly changed.

These regularities have been revealed in a study of partially methylated β-D-glucopyranosides since in this case it is clear which of the hydroxyl groups participate in complex formation.



XVII

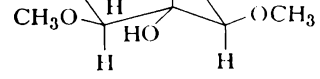


XVIII

If compound XVII is added to the solution of a copper salt, the resistivity is greatly increased, which is an indication of a considerable complex formation. A complex is formed due to the hydroxyl groups at C-3 and C-4; the angle between them in the normal conformation is 60°, and both OH groups in the complex must be made to lie in a single plane. This leads to the distortion of the conformation and to a considerable change in the optical rotation. The dextrorotatory complex increases the rotation $[M]_D$ by $+2190°$ as compared with the starting compound XVII.

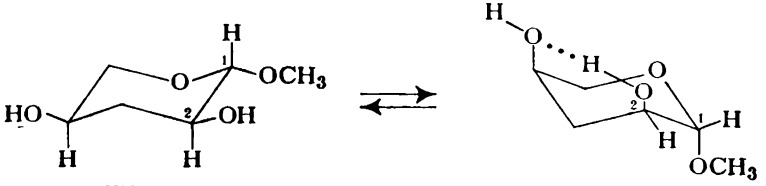
The strong fall of electrical conductivity caused by the addition of compound XVIII to the solution of the copper salt is also evidence of the formation of a complex. The hydroxyl groups at C-2 and C-3 participate in this process, and the rotation is strongly changed (for the reasons given in the discussion of the behaviour of compound XVII). The levorotatory complex alters $[M]_D$ by $-1990°$.

Compound XIX changes the electrical conductivity but slightly, and the rotation is also slightly changed; the change of $[M]_D$ is only $-83°$. The hydroxyl groups at C-2 and C-4 (C-6) or at C-4 and C-6 cannot thus give a complex with copper compounds.



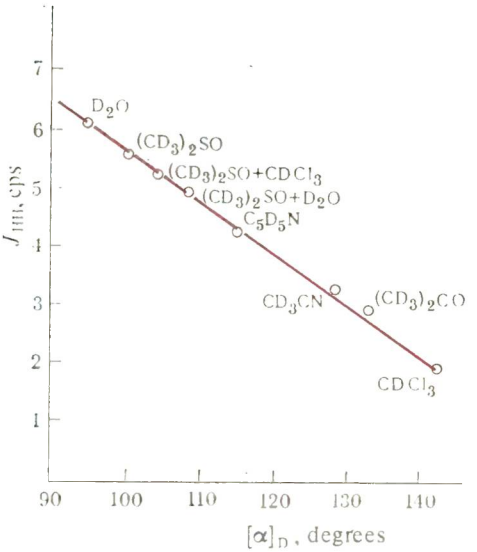
XIX

An interesting relationship has been found (5) between the conformation of glycosides (estimated by the spin-spin coupling constants of protons at C-1 and C-2 in the NMR spectra)



XXa XXb

Figure 11.1.




*The optical rotation versus spin-spin coupling constants for the series of pyranosides in various solvents.*

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and the optical rotation at the sodium D-line (Fig. 11.1).

The Brewster calculation gives, in the case of 3-deoxy-β-L-erythro-pentapyranoside, $[\alpha]_D = +137°$ for the triaxial form **XX**b and $[\alpha]_D = +100°$ for the triequatorial form XXa; the first value coincides with $[\alpha]_D = +142°$ in $CHCl_3$ solution, and the second, with the $[\alpha]_D = +95°$ found in water. Thus, in a non-polar solvent, there predominates the triaxial form XXb stabilized by the anomeric effect and intramolecular hydrogen bonding. When passing to aqueous solutions this intramolecular hydrogen bonding is broken, the repulsion of two axial oxygen atoms predominates over the anomeric effect, and the equatorial conformation XXa becomes more favourable.

The use of NMR spectroscopy has made it possible to detect, in particular, conformational changes during the formation of borate complexes (6). Interesting results have been afforded by the study of the optical rotatory dispersion in the presence of borax (7) or molybdenic acid (8). The application of modernized instruments has enabled direct measurements of the Cotton effect of carbohydrates in the region of 170 nm (9).

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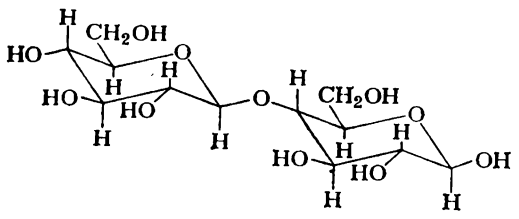
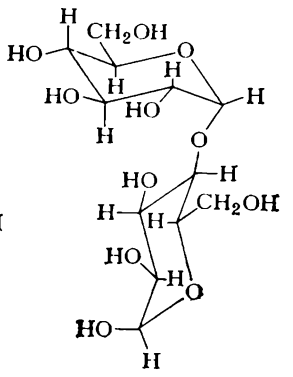
Two important polysaccharides, cellulose and starch, are, from the stereochemical standpoint, examples of two types of high-molecular-weight compounds: linear rodlet-like and globular (sphere-shaped) polymers. Both polymers are made up of glucose units, and the problem of the sharp difference in the properties of the polymers has long been tackled by scientists.

On careful hydrolysis there can be isolated the intermediates—cellobiose from cellulose and maltose from starch and glycogen. The disaccharides indicated are built up of two glucose molecules joined together by a linkage of the ether type. All the difference between cellobiose and maltose boils down to a single stereochemical detail: cellobiose XXI has a β-glycosidic linkage and maltose XXII an α-glycosidic linkage.



XXI



XXII

Not long ago the differences in properties between cellulose and starch were reduced to this stereochemical detail and the indicated compounds were cited as examples demonstrating how subtle stereochemical differences could give rise to compounds having quite different properties. Based on the conformational concepts, one can understand that the formation of the linear macromolecule of cellulose is due to the β-glycosidic linkage and that of the coil-like molecule characteristic of starch is due to the α-glycosidic linkage. This tendency for the formation of a coil in the starch molecule is enhanced also by the fact that the starch macromolecule (more exactly, its main constituent part—amylopectin) has a branched structure.

Cellulose and starch are typical representatives of two types of high-molecular-weight compounds—with linear (rod-like) and globular (sphere-shaped) molecules. The cellulose macromolecule has a rodlet-like configuration, about 1.5μ long. With such a length it could have

been seen under the microscope if the thickness of the filament (0.5 mμ) had not been much smaller than its length. Compounds of this kind, with thread-like molecules, can readily assume the fibrous structure; when dissolved they swell and form viscous solutions. The amylopectin molecule has a spherical shape, owing to which the compound can dissolve without swelling, with the formation of solutions of relatively low viscosity.

Interesting features have been revealed in the spectropolarimetric investigation of polysaccharides: in their presence the absorption band of iodine or dyes becomes optically active due to their adsorption on an optically active "template" (10).

Stereochemical features determine the properties of other polymers as well: the well-known examples are isotactic polystyrene and polypropylene, natural rubber with its *cis*-structure of the polymeric chain. We shall not delve into the details of the stereochemistry of synthetic high-molecular-weight compounds; for a detailed study of this subject, the reader is referred to the literature (1 and 11).

## 11.2. THE SPATIAL STRUCTURE OF PROTEINS

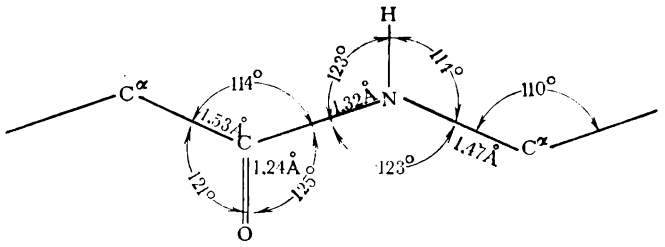
As early as the time of Pasteur it was known that proteins exhibit optical activity. Later, it was found that this is due to the optical activity of the amino acids that make up proteins. As configurational investigations were progressing it was established that the amino acids contained in proteins have the same spatial configuration and belong to the L-series. Only a few exceptions are known, the character of which more strongly supports the rule. The "non-natural" spatial isomers of amino acids have been found to be contained in certain antibiotics and in bacteria.

At present, organic chemistry has approached the stage of the more thorough study of individual proteins and of the elucidation of all the details of their chemical constitution.

The sequence of arrangement of the amino-acid residues (the amino-acid sequence) in the polypeptide chain creates the **primary structure** of a protein; it has been established at present for a number of natural proteins. The synthesis of a number of proteins has also been effected; examples are insulin (51 amino acids), ribonuclease (124 amino-acid residues). Syntheses of this kind require that hundreds of chemical reactions be carried out successively. Of great help in this respect is the method of solid-phase synthesis proposed by Merrifield in 1963: the polypeptide chain is gradually built up on small, solid beads of a polymer (polystyrene resin) and is removed from the polystyrene support only after the synthesis is complete.

The properties of proteins are governed not only by the amino-acid sequence but also by the spatial structure of the protein molecule, in

Figure 11.2.




*The interatomic distances and bond angles in the peptide chain.*

particular, by its **secondary structure**, which is the conformation of the polymer chain of proteins (for a detailed treatment of the secondary structure, see ref. 12).

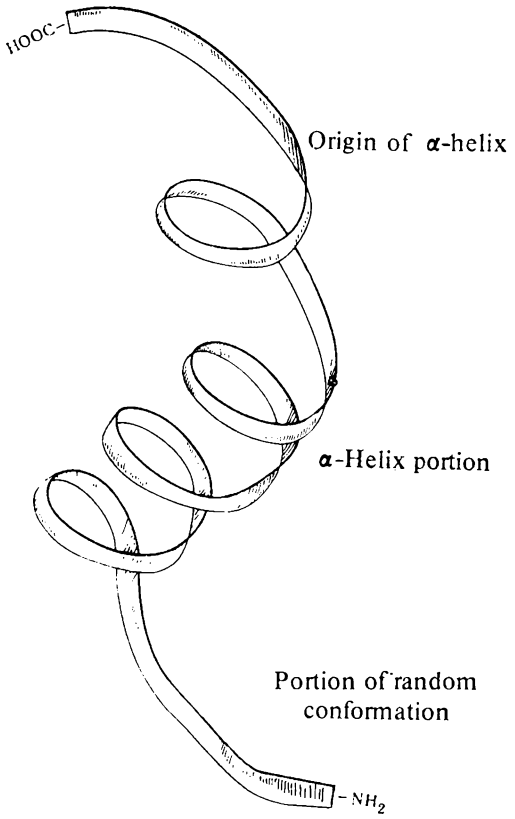
The basic structural unit of the polypeptide chain is the **peptide linkage,** a link of the secondary-amide type. The valence angles and interatomic distances (bond lengths) shown in Fig. 11.2 have been determined for the peptide link by means of X-ray diffraction analysis. The investigation of the dipole moments and other properties has shown that the peptide group has, as a rule, the transoid conformation in proteins. Exceptions are compounds in which the grouping —CO—NH— is part of a ring with a small number of members and which can therefore exist only in the *cis*-form.

In 1951 Pauling advanced, as a model of the spatial structure of protein molecules, the so-called α-helix, in which the polypeptide chain is represented as a thread wound round the cylinder surface. The adjacent turns are arranged so that there are hydrogen bonds between the NH and CO groups in different turns (Fig. 11.3). There are 3.6 amino-acid residues for each turn of the helix. The degree of extension of the helix depends on the nature of the protein and the external conditions. Thus, for example, poly-L-alanine begins assuming the α-helical conformation in pure water if the polypeptide chain contains more than 10 turns. In the presence of inorganic salts the helix is better stabilized due to hydrophobic interactions.

Another orderly conformation is the β-structure (the β-helix) in which the polypeptide chains are arranged in parallel in an extended zig-zag pattern and are also linked by hydrogen bonds which are now formed between the amino-acid residues of different chains.

Proteins may also adopt a random, disordered conformation. This is especially favoured by solvents capable of breaking up hydrogen bonds stabilizing the α-helix.

Figure 11.3.




*The α-helical conformation of a polypeptide.*

A very sensitive method of investigation of the conformations of proteins and polypeptides is spectropolarimetry. In the random conformation, the character of optical rotation of proteins is determined primarily by the amino-acid composition, the optical rotatory dispersion curves being smooth. When a protein assumes the α-helical conformation, there appears an additional great contribution from this helical structure, the optical rotatory dispersion may become anomalous, and the Cotton effect appears at 233 nm (13). By observing the changes in the ORD curves, depending on the pH value, the nature of the solvent and temperature, one can draw conclusions as to the conformation

of proteins and, in particular, calculate the fraction of the α-helical structure.

Thus, the optical activity of poly-L-glutamic acid has been studied (14) and it has been found that when the pH value changes from 7.0 to 4.5, there occurs a reversible change of $[\alpha]_{546}$ from —120° to —8°. This is compared to the change of optical rotation observed upon denaturation of certain proteins.

The spectropolarimetric method has been employed for studying the conformational changes caused by the introduction of additional peptide chains into the insulin molecule at its three free amino groups (15). The original insulin is helical by 25 per cent, modified with lysine by 32-33 per cent and with glutamic acid by 3-16 per cent. If certain dyes (acridine orange, pseudoisocyanine) are added to solutions of synthetic polyglutamic acid and the optical rotatory dispersion is measured in the region of 560-360 nm, then at pH = 5.5 the ORD curve is smooth (the polymer in the random conformation); at pH lower than 5.1 when the polymer assumes the helical conformation, the optical rotatory dispersion becomes anomalous, in which case the magnitude of rotation sharply increases. This is associated with the adsorption of a dye on the helical polypeptide chain, as a result of which the absorption band of the dye becomes optically active (16). The subsequent development of the spectropolarimetric method has made it possible to measure directly the Cotton effect in the region of 185-240 nm, which is associated in a straightforward manner with the helical structure of the molecules of proteins and polypeptides (for a detailed treatment, see ref. 17).

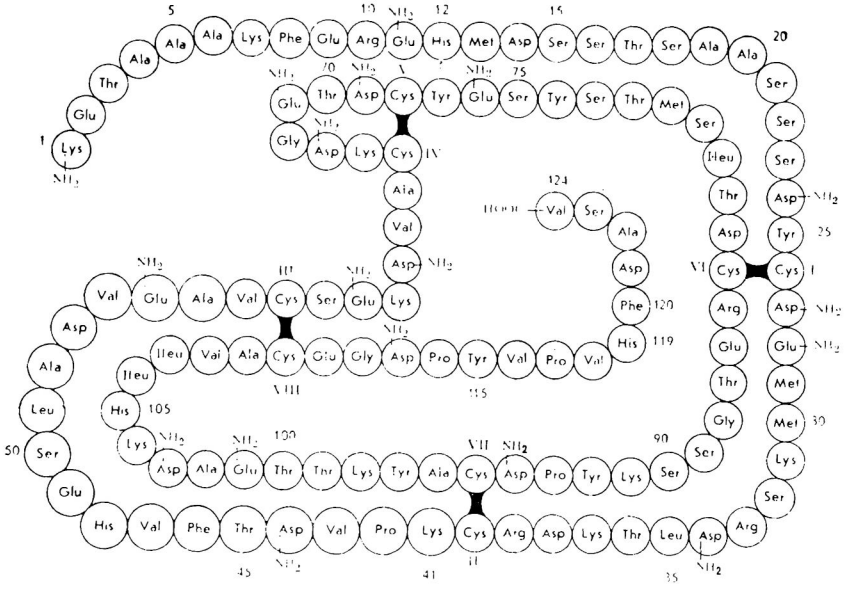
Evidently, not all the changes of the ORD curves of polypeptides and proteins can be explained by the conformational changes. This is demonstrated, for example, on models of simple amides (18) and also on models of acylamino acids (19).

A special system has been worked out by the IUPAC Commission on biochemical nomenclature for designating the conformations of polypeptide chains (20).

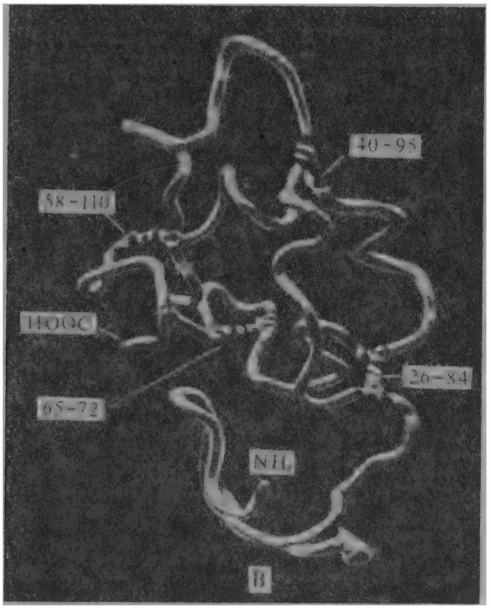
A characteristic feature of conformational interconversions in molecules of proteins and nucleic acids is their cooperation. It means that a conformational change in one of the segments of the macromolecule causes analogous conformational changes in the neighbouring segments and, in the final run, in the entire macromolecule. This cooperation increases with increasing length of the macromolecular chain. Transformations of this kind are of great importance in biochemical processes. Cooperative conformational changes have been considered in detail by Engel and Schwarz (21).

The polypeptide chain having the shape of the α-helix, the β-structure or random conformation may assume one more form—**the tertiary structure.** It is this structure that determines, to a considerable extent, the specific biological properties of each individual protein. The so-called

Figure 11.4.

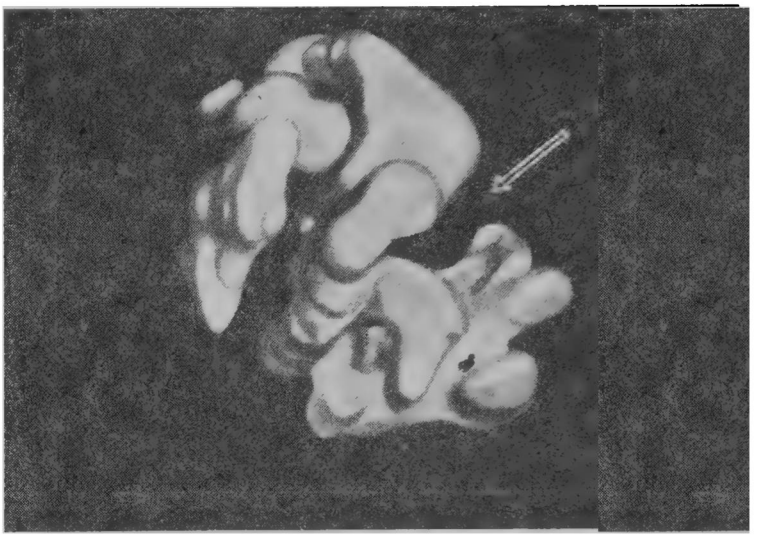

Lys Glu Thr Ala Ala Ala Lys Phe Glu Arg Glu His Met Asp Ser Ser Thr Ser Ala Ala Ser Ser Ser Ile Thr Asp Tyr Cys Cys Arg Asp Glu Glu Thr Met Met Lys Ser Arg Asp Lys Thr Leu Asp Lys Cys Arg Asp Pro Pro Glu Val Val Asp Ala Ala Asp Phe His Cys Cys Ser Glu Lys Val Ala Cys Glu Gly Asp Pro Tyr Val Pro Val Ile Leu His Lys Asp Ala Glu Thr Thr Lys Tyr Ala Cys Asp Pro Tyr Lys Ser Val Phe Thr Asp Val Pro Lys Cys Asp Ala Leu Ser Glu His Val Ala Ser Ala Tyr Ser Thr Ser Ala Ala Ser Ser Ser Ile Thr Asp Tyr Cys Cys Arg Asp Glu Glu Thr Met Met Lys Ser Arg Asp Lys Thr Leu Asp Lys Cys Arg Asp Pro Pro Glu Val Val Asp Ala Ala Asp Phe His Cys Cys Ser Glu Lys Val Ala Cys Glu Gly Asp Pro Tyr Val Pro Val Ile Leu His Lys Asp Ala Glu Thr Thr Lys Tyr Ala Cys Asp Pro Tyr Lys Ser Val Phe Thr Asp Val Pro Lys Cys Asp Ala Leu Ser Glu His Val

A




***The structure of ribonuclease:***
*A—amino-acid sequence; B—three-dimensional model (according to X-ray diffraction data; the amino-acid residues joined together by disulphide bridges are numbered).*

Figure 11.5.



*The model of the lysozyme molecule.*

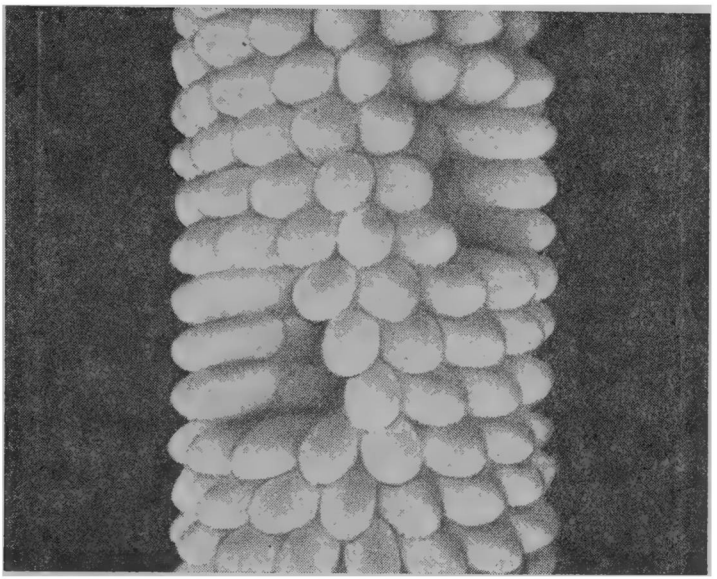
denaturation, i.e., the loss of the specific properties of a natural protein, is primarily associated with the changes of the tertiary (and also the secondary) structure.

The tertiary structure of the polypeptide chain is governed in the first place by the primary structure of the protein molecule; besides, it is affected by the solvent, the pH of the medium, temperature, and by the presence of various chemical agents. The structures of natural polypeptides obtained synthetically assume spontaneously, after the "natural conditions" (the pH of the medium, temperature) are created, the secondary and tertiary structures usual for a given natural sample.

Natural proteins adopt, as a rule, the thermodynamically most favourable conformation, the energy of which is found to be minimal with account taken of a number of steric interactions—van der Waals forces, hydrophobic attraction (which arises primarily between aromatic rings and also between aliphatic hydrocarbon radicals), hydrogen bonds, electrostatic attraction or repulsion of the charged groups. An important part in the formation of the tertiary structure is also played by the closure of the disulphide bridges between cystein residues.

An example is the molecule of ribonuclease, the tertiary structure of which is fixed by four disulphide bridges (Fig. 11.4). If native ribonuclease (i.e., ribonuclease that has retained its natural properties and, in partic-

Figure 11.6.



*The model of the tobacco mosaic virus (the pear-shaped figures are subunits).*

ular, catalytic activity) is treated with urea and mercaptoethanol, the disulphide bridges are broken—there takes place denaturation with loss of biological activity and change of the tertiary structure. After the reagents responsible for the denaturation are removed ribonuclease again closes its disulphide bridges under the influence of the oxygen of the air, assuming a characteristic tertiary structure and regaining its biological activity.

The decisive role in the elucidation of the tertiary structure of proteins was played by X-ray diffraction analysis which in 1957 allowed the English investigator Kendrew to determine for the first time the tertiary structure of myoglobin. In subsequent years, X-ray structure analysis was used to establish the spatial structure of many other proteins and to relate it to their biological functions. Thus, the molecule of lysozyme, an enzyme that splits up polysaccharides, has the three-dimensional structure shown in Fig. 11.5. The arrow shows a cavity which is the active centre of lysozyme; it is this site that the molecule of a polysaccharide to be split up approaches.

Several protein molecules, either identical or different (subunits), can unite with one another; in this way there arises the **quaternary structure** of the protein. For example, the molecule of hemoglobin consists of four

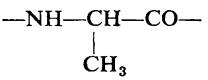
subunits; under the action of urea it is split into two non-identical parts, which after the reagents are removed can again unite with each other, reproducing native hemoglobin. Another protein, the tobacco mosaic virus, is composed of more than two thousand subunits (Fig. 11.6).

Additional data on the spatial structure of proteins are available in the literature (22).

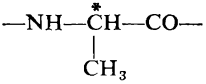
## 11.3. CYCLOENANTIOMERISM

A peculiar type of molecular asymmetry of polypeptide structures has been created by Prelog and coworkers (23).

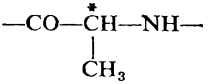
This type of molecular asymmetry called **cycloenantiomerism** was treated in the works of Prelog in a general form; it will be more spectacular if we consider it using a concrete example. Let us consider a cyclopeptide, cyclohexaalanine, which is built up of equal numbers of (+)-alanine and (—)-alanine residues. The alternation of the (+)- and (—)-alanine residues in the cyclopeptide may vary; this may include, in particular, an unsymmetrical arrangement. Before representing it we are to choose the designations. The (+)-alanine residue will be designated as a filled (red) circle, and the (—)-alanine residue, as an unfilled (white) circle. Since each of the residues



has the NH group on one side and the CO group on the other, it is not immaterial how they are arranged in the ring: in the form of unit I or II:



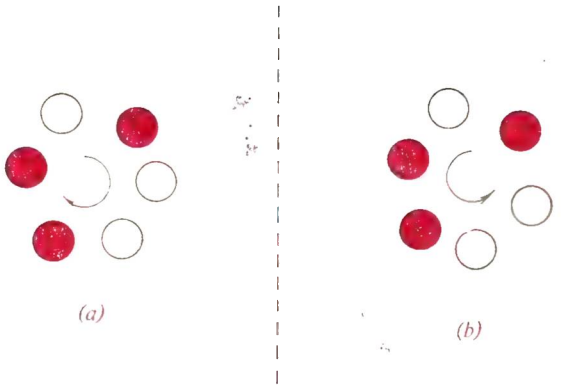
I



II

The direction of the round is indicated by an arrow. Let us now picture the cyclopeptide of interest and its mirror-image antipode (Fig. 11.7). When drawing the mirror-image one should take into account that the configuration of the asymmetric centre in each unit is reversed (therefore the red filled circles turn into unfilled white circles and vice versa), and the direction order of circumvention by-passing, i.e., the direction of the arrow, is also changed. The result seems to be unexpected at first glance: the disposition of the red and white circles in

Figure 11.7.



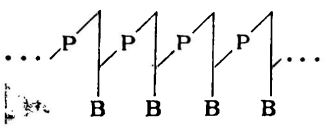

*The cycloenantiomerism of cyclohexaalanine.*

both figures is found to be the same; they differ only in the direction of the arrows. Figures *a* and *b* are a pair of cycloenantiomers.

Having carried out the appropriate syntheses, Prelog and coworkers actually produced a pair of optical antipodes having structure *a* and *b*. They have a rotation of $[\alpha]_{578} = \pm 23°$; when being mixed, they give a racemate, like any other pair of optical antipodes, and on hydrolysis each of the antipodes is converted into *optically inactive* racemic alanine since either of the molecules contains three (+)-alanine residues and three (—)-alanine residues.

## 11.4. NUCLEIC ACIDS

As early as 1871 there were reported the first data showing that cellular nuclei contain organic substances, whose molecules are characterized by the presence of nitrogen and phosphorus. Later, these substances were termed nucleic acids. It was shown that they are polymers that contain heterocyclic bases (adenine, guanine, cytosine, uracil, thymine, and sometimes other bases), a pentose (ribose or deoxyribose) and phosphoric acid. The general structure of nucleic acids may be represented by the following scheme (the vertical line denotes pentose residues, B stands for heterocyclic bases, and P designates the phosphodiester groups):



Thus, a polymer is a chain in which the pentose and phosphoric-acid residues alternate and heterocyclic bases form side "branches".

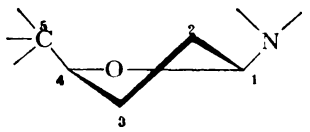
The study of nucleic acids had not been very intensive for many decades. Textbooks on biochemistry published in the 1940s described nucleic acids as compounds, the precise structure and the biological role of which had not yet been clarified. But the end of the forties and the beginning of the fifties marked a turning point: the nucleic acids were found to be of prime importance in heredity and protein biosynthesis and X-ray structure studies detailed their structure (24).

Depending on the nature of the carbohydrate residue, a distinction is made between deoxyribonucleic acids (DNA) which contain 2-deoxyribose, and ribonucleic acids (RNA) containing ribose.

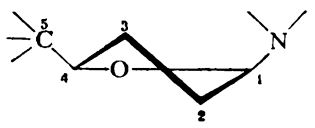
The monomeric units of nucleic acids are **nucleotides** consisting of a heterocyclic base, a pentose, and a phosphoric-acid residue. When phosphoric acid is eliminated, a nucleotide is converted into a **nucleoside**, which contains only two components—a heterocyclic base and a pentose.

The spatial structure of nucleotides is determined by the shape of the pentose ring, the disposition of the heterocyclic base relative to the pentose and by the conformation of the phosphate-ester linkage. Of the many possible geometric forms there are selected only strictly definite, energetically favourable conformations. The following information is now available on the spatial structure of the separate constituents of nucleic acids and of their molecules as a whole (25).

The carbohydrate residue has the half-chair or envelope conformation: two forms are encountered most frequently:



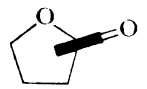

$C_2$-*endo*




$C_3$-*endo*

The heterocyclic base (denoted by a thick line) may assume two most stable conformations with respect to the pentose:

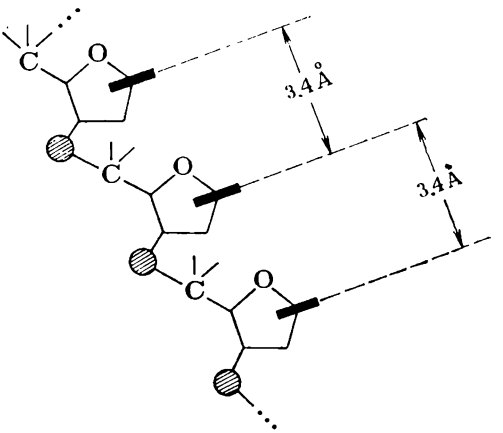
*syn-*




*anti-*

The phosphate-ester linkage has a conformation that provides the approach of the heterocyclic bases of adjacent nucleotides to a distance

of 3.4 Å: a stacking interaction occurs between the rings due to hydrophobic forces. As a result, the heterocyclic bases are "overlapped", forming a hydrophobic nucleus on the external side of which there are arranged hydrophilic phosphate groups and sugar residues. This may be represented schematically as follows:




Such an interaction has also been traced out on model compounds (see, for example, ref. 26).

According to the celebrated Watson-Crick model (27), nucleic acids form a double helix consisting of two chains in which the heterocyclic bases of one chain are linked through hydrogen bonds to the heterocyclic bases of the other chain. The adenine or guanine residue is found to be invariably linked to the uracil or cytosine residue, respectively. Both combinations are almost the same in size, and therefore, in spite of their alternation, the polynucleotide chain is highly sterically regular.

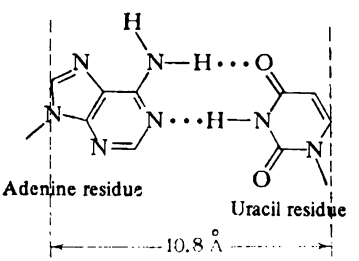
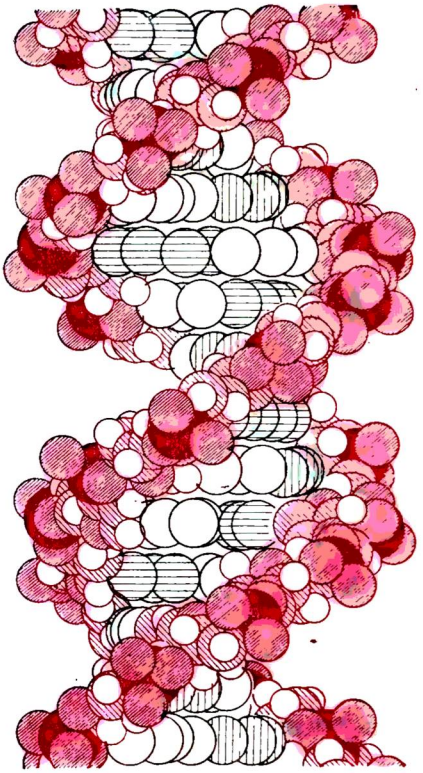


Figure 11.8.



*The Watson-Crick model of deoxyribonucleic acid (DNA).*

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The model of deoxyribonucleic acid is shown in Fig. 11.8. The internal hydrophobic part is formed by pairs of heterocyclic nuclei, between which there also takes place a stacking interaction. The hydrophilic deoxyribose residues and the phosphate groups that join them are arranged around the nucleus along the right-hand helix.

The elucidation of the biological role of nucleic acids as heredity carriers and protein-synthesis regulators laid up the foundation for the development of a new branch of science, molecular biology. The mechanism of protein synthesis has been rather thoroughly disclosed, but the discussion of these problems would lead us too far beyond the scope of this book.

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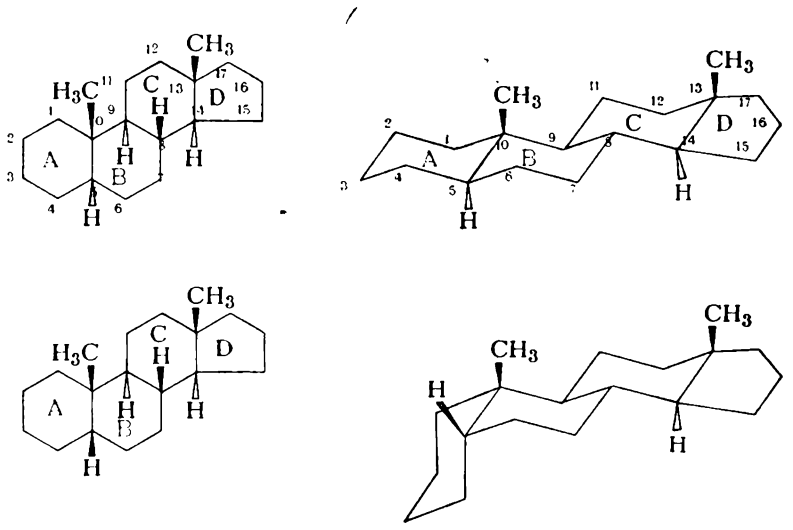
## 11.5. STEROIDS

Steroids constitute a large and important group of natural compounds which predominantly play the part of hormones in the organism. The basic structural unit of these compounds is the polycyclic structure of cyclopentanoperhydrophenanthrene. Among natural compounds there are most frequently encountered two stereoisomeric forms having the 10,13-dimethylcyclopentanoperhydrophenanthrene skeleton, which are represented by the formulas given below.

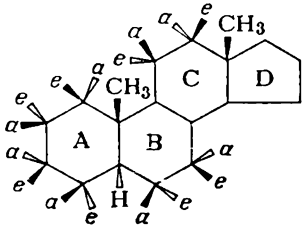
This structure has the trivial name androstane (for the nomenclature of steroids, see ref. 28).



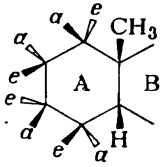

The two cyclic systems differ by the mode of fusion of rings A and B: the first of them has the *trans*-junction (just as in *trans*-decalin) and the second, the *cis*-union similar to that in *cis*-decalin. The remaining ring junctions in both stereoisomers are identical and belong to the *trans* type.

As known, the positions of substituents in steroids are conventionally designated by the letters α- (if the substituent sticks out below the plane of the drawing) and β- (if the substituent sticks out above the plane of the drawing). There is no unambiguous correspondence between the α- and β-notation and the axial and equatorial orientation. In the series of 5α-compounds, to the substituents in the various positions there corresponds the orientation shown in scheme XXIII, and in compounds

of the 5β-series only the orientation in the ring A is different (scheme XXIV):



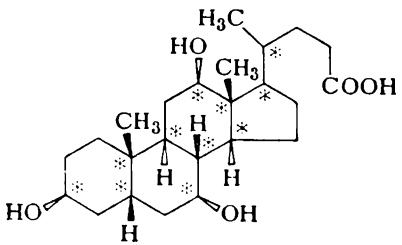

XXIII




XXIV

All the six junction atoms of cyclopentanoperhydrophenanthrene are asymmetric and therefore for the unsubstituted hydrocarbon the number of stereoisomers is $2^6 = 64$. When substituents appear in the non-junction positions, the number of possible stereoisomers increases even more. However, as has been said earlier, only a few of the possible stereoisomeric forms are encountered in natural compounds.

The high stereoselectivity of the syntheses of steroids that occur in living organisms, is vividly illustrated, for example, by the fact that of the 2048 spatial isomers possible for compounds with eleven asymmetric atoms only one stereoisomer of cholic acid XXV is found in living organisms:




XXV

The conformational rigidity of the steroid skeleton considerably simplifies the unravelling of the regularities that relate the spatial structure, primarily the conformational disposition of the substituents (axial or equatorial), to their spectral and other physico-chemical characteristics and also to the reactivity. Therefore, apart from their biological functions, steroids have been and still are favourite models in theoretical investigations in organic chemistry and also in the development of new physico-chemical methods. The regularities disclosed on conformationally fixed

steroid models are then extended to other compounds. Thus, for example, the rule according to which in the IR spectra the valence vibrations of the C—X bond with the equatorial orientation of substituent X have a higher frequency than the analogous vibrations with the axial orientation of the substituent has been worked out exactly on steroidal compounds (Table 11.1).

TABLE 11.1. THE FREQUENCIES OF THE VALENCE VIBRATIONS OF THE C—X BOND IN IR SPECTRA OF X-DERIVATIVES OF CYCLOHEXANE

| Type of C—X bond | Frequency, $cm^{-1}$ | | Type of C—X bond | Frequency, $cm^{-1}$ | |
|---|---|---|---|---|---|
| | for axial X | for equatorial X | | for axial X | for equatorial X |
| C—D | 2146 | 2174 | C—OH | 996-1036 | 1037-1044 |
| C—F | 1020 | 1053 | C—$OCH_3$ | 1086-1090 | 1100-1104 |
| C—Cl | 688 | 742 | C—$OCOCH_3$ | 1013-1022 | 1025-1031 |
| C—Br | 658 | 685 | O—H* | 3637-3639 | 3629-3630 |
| C—I | 638 | 654 | | | |

* For the vibrations of the O—H bond, the frequency ratios often do not obey the rule!

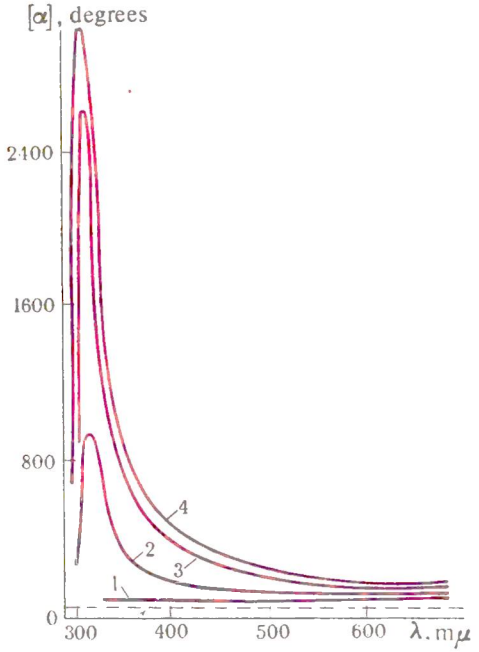
The regularities concerning the reactivity of axial and equatorial substituents, which have been found for steroids (see Chapter 5), enable a deeper understanding of the reactivity of mobile cyclohexane compounds, where the picture is complicated by the coexistence of different conformations.

The **spectropolarimetric method** was developed in investigations using steroids. The samples used in the first studies carried out by Djerassi (29) were ketones of the steroid series. These compounds are particularly convenient for studies since they have an optically active absorption band in the region of about 300 nm, the absorption of this band being not great, which makes it possible to carry out rotation measurements directly in the absorption region by recording the Cotton effects.

The character of the ORD curves of ketosteroids depends on the position of the carbonyl group in the ring and the way in which the rings are fused together. Let us consider, as an example, the ORD curves of androstane and its three keto derivatives (Fig. 11.9).

The optical rotation of androstane remains almost unchanged in the region of 300-700 nm, as should be expected for an optically active saturated hydrocarbon, the absorption bands of which lie in the far ultraviolet region of the spectrum (below 200 nm). If the keto group is in position 3, there appears a peak on the ORD curve in the region of 300 nm, which is due to the optically active carbonyl absorption band.

Figure 11.9.




*The ORD curves of androstane (curve 1) and its 3-oxo- (curve 2), 17-oxo- (curve 3) and 3,17-dioxoderivatives (curve 4).*

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An analogous peak, but with a higher amplitude, is produced on the ORD curve by the keto group situated in position 17. On the ORD curve of 3,17-androstandione, the amplitude of the Cotton effect corresponds approximately to the sum of the effects observed for 3-keto- and 17-ketoandrostanes.

Characteristic ORD curves are also displayed by ketosteroids with the keto function in other positions. Having studied the optical rotatory dispersion of a very large number of steroidal compounds, Djerassi was able to formulate a rule which states that the shape of the ORD curve is not substantially changed when substituents having the nature of optically weak chromophores are introduced into a ketosteroid provided that the immediate stereochemical environment (the configuration and conformation near the steric centre responsible for the creation of carbonyl anomaly) remains unaltered. Basically, this is a more special case of the Chugaev distance rule.

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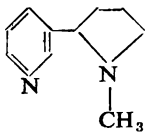
Further examples of the application of spectropolarimetry to the study of steroids are available in the literature (30).

With the use of liquid crystals formed by certain derivatives of cholesterol, a new spectroscopic technique has been developed: the absorption bands of optically inactive compounds mixed with such liquid crystals assume optical activity (31).

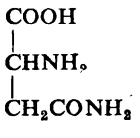
## 11.6. STEREOSPECIFICITY OF BIOCHEMICAL REACTIONS

The optical antipodes (enantiomers) of a compound, which are indistinguishable in their ordinary physical and chemical properties, more often than not differ sharply from each other by their physiological effect. This aspect has been treated in detail by Beckett and Golikov *et al.* (32, 33). Thus, the tobacco alkaloid, levorotatory nicotine XXVI, is much more (by several times) poisonous than dextrorotatory nicotine; dextrorotatory asparagine XXVII has a sweet taste and its optical antipode is tasteless. Natural L-glutamic acid XXVIII has the taste of meat (is used as a flavouring intensifier in the preparation of food concentrates), whereas D-glutamic acid is tasteless.

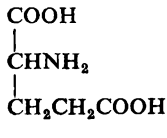
Of the two antipodes of adrenaline XXIX the levorotatory isomer exhibits a stronger hormonal effect. Only one of the four diastereomers of chloromycetin (chloramphenicol) XXX, the levorotatory *threo*-somer, is an active antibiotic, the other stereoisomers being completely nactive.



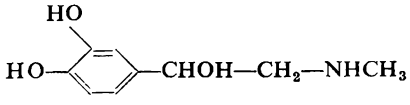
XXVI



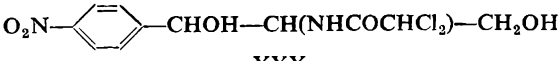
XXVII



XXVIII



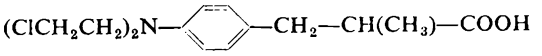
XXIX



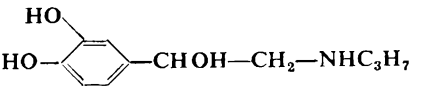
XXX

The levorotatory form of sarcolysine XXXI is active for treatment of certain kinds of tumors, whereas the dextrorotatory form is inactive.

The dextrorotatory isopropylnoradrenaline XXXII has a much stronger (by 800 times) bronchodilating effect than the levorotatory isomer.

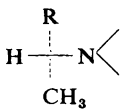


XXXI

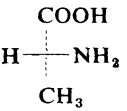


XXXII

The synthetically obtained antipode of natural (—)-morphine has no analgesic activity (pain-releasing effect). It has been found that analgesics of configuration XXXIII comparable with the configuration of D-alanine XXXIV are generally more active.

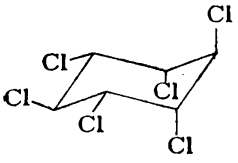


XXXIII

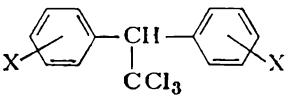


XXXIV

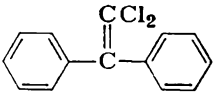
Insecticide preparations also display stereospecificity. A well-known example is hexachlorocyclohexane, of the eight spatial isomers of which only one, the so-called γ-isomer XXXV has strong insecticide activity. In investigating a series of insecticide preparations it has been found that there is a relationship between the insecticide action and the possibility of free rotation in molecules — the analogues of the well-known insecticide preparation DDT. It has been established that if in compounds of the type XXXVI the substituents X are in the *ortho*-positions, the insecticide activity diminishes; rigid compounds of the type XXXVII are also inactive.



XXXV



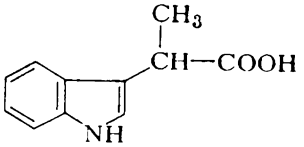
XXXVI



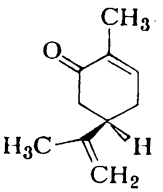
XXXVII

The activity of growth stimulants is also often associated with their spatial structure. For example, (+)-α-3-indolylpropionic acid XXXVIII

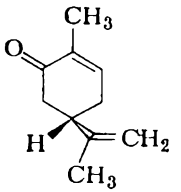
is 30 times more active than the (—)-isomer; *cis*-cinnamic acid is capable of accelerating the growth of plants, whereas *trans*-cinnamic acid is inactive in this respect. Differences in odour have also been noticed for optical antipodes, say, for those of carvone XXXIX (34).



XXXVIII



XXXIXa
Odour of caraway



XXXIXb
Odour of mint

The examples given, like many others, provide evidence that the fine details of the structure of organic compounds, which manifest themselves, in particular, in the form of such a specific and "abstract" property as optical rotation, are of great importance for biochemical processes. The point here is not of course that living organisms react differently to the right- or left-handed rotation itself: it serves only as a sign that makes it possible to differentiate between the antipode configurations.

The true factor actually responsible for differences in physiological effect is the difference in spatial structure, i.e., in configuration. It is believed that the following three factors may be responsible for these differences.

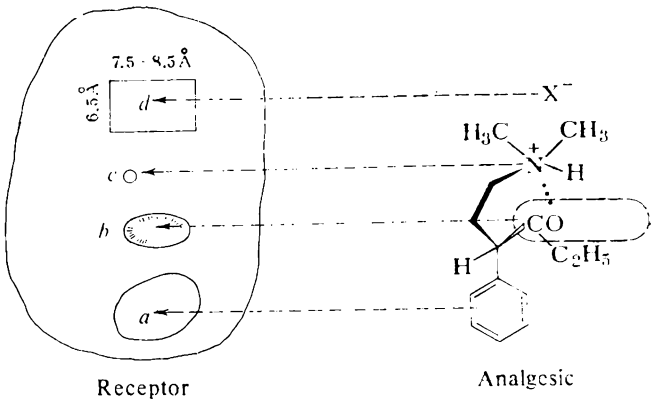
1. The difference in the distribution in tissues. For instance, (+)-mandelic and (+)-α-naphthylacetic acids are adsorbed by wool and casein more strongly than their optical antipodes. Specific membrane systems are known, which increase the concentration of L-amino acids inside cells by about 500 times as compared with the medium.

2. The difference in the affinity of isomers for the receptor (i.e., a substance which is acted on by these isomers in the organism). Such a difference may arise since for asymmetric structures it is important whether they interact with one or the other of the optical antipodes.

3. The difference in properties between the complexes formed by (+)- and (—)-isomers with the receptor.

The factor responsible for the stereospecificity of the biological effect consists, in the long run, in that living organisms themselves are composed of an optically active asymmetric material. A graphic analogy for this phenomenon was given by Pasteur. If we drive in a screw into a board with straight fibres, the "antipode" screws, the left-hand and the right-hand thread, will enter the board with the same ease. But if

Figure 11.10.




*The geometry of the molecules of analgesics:*
*a — flat portion of the receptor ; b — cavity ; c — centre of the charge ; d — site for the anionic group*

the screw is to be driven into a threaded hole, then it can be done only if the direction of threading is the same in the screw and in the hole.

Scientists have now passed over from general considerations to the study of the mechanism of the biological action of concrete preparations. As an example, let us consider the action of analgesics—morphine and its substitutes. The rigidity of the morphine molecule has made it possible to create a plausible model of the receptor—a portion with which morphine interacts, and then to determine the molecular geometry of analgesics required for the manifestation of the morphine-like effect (**Fig. 11.10**).

The decisive role in the stereospecificity of biochemical processes is played by the presence of stereoselective catalysts, or enzymes, in a living organism. For example, the selectivity of enzymes causing fermentation manifests itself in that only the epimeric sugars, glucose and mannose (and the corresponding ketohexose—fructose), are capable of fermentation.

Owing to the high effectiveness and selectivity of the action of enzymes, they can be used to carry out many important chemical transformations. Fermentative processes form the basis of a number of branches of industry, the oldest and the most famous of which is the production of alcohol by the fermentation of sugar compounds. Various kinds of microorganisms are used to prepare lactic acid, acetone, butanol, and many other products. The hydrocarbons contained in petro-

leum are processed microbiologically into a protein mass suitable as food for animals.

Apart from these, so to say, "crude" microbiological processes, which lead to the preparation of simple organic compounds, fine transformations effected by microbiological methods have become increasingly important over the last several decades; these are the syntheses of vitamins, hormones, antibiotics (for a review, see ref. 35).

## 11.7. THE PROBLEM OF THE ORIGIN OF PRIMARY ASYMMETRY

Optical activity is an integral property of the most important natural compounds. The role of optically active substances in living nature is so great that searches for optically active substances on other planets are considered today to be one of the possible ways to detect extraterrestrial life (36).

Much attention has been drawn, for example, to optically active substances that are claimed to have been found in meteorites. The inspection has shown, however, that this was associated with the errors inherent in spectropolarimeters during the measurement of specimens of high optical density (37). And when *racemic* amino acids were detected in the meteorite that fell in 1969 on the territory of Australia, this was interpreted as an indication of their non-biological origin.

Living organisms are capable of constantly producing asymmetry, i.e., of transforming optically inactive substances into optically active ones. This circumstance drew the attention of Pasteur: in his paper in 1860 he advanced the opinion that the asymmetry of molecular structure might possibly be the only distinct boundary line separating the chemistry of living matter from that of the inanimate nature. This suggestion, which was correct in itself, was used by some scientists to advance idealistic, vitalistic theories of the origin of optically active substances. The vitalists believed that optical activity could *never* arise without the participation of factors associated with living nature; according to their opinion, there are no "natural" ways for the ultimate origin of optically active organic compounds. By their theory, primary asymmetric substances appeared in a certain mysterious, supernatural way.

The vitalistic views on the origin of optically active substances were most clearly put forth in 1898 by Japp in his presidential speech at a meeting of the British Scientific Association: "An optically active molecule could be generated only through the agency of the living force". This speech caused an animated dispute on the pages of the London journal "Nature". However, no one of those who objected to the Japp's statement indicated in which way primary asymmetry had originated in nature since nobody knew the actual routes at that time.

Pasteur tried to induce asymmetry in growing crystals by placing them in the field of a powerful magnet or by carrying out reactions in rapidly rotating vessels. He also made an attempt to cause the reversal of the sign of rotation in natural compounds by growing plants under the influence of the mirror-reflected sunlight as though the Sun rose in the West and set in the East. No positive results were obtained by him.

In the 1890's, Boyd also tried with no effect to "induce" optical activity by conducting, in a powerful magnetic field, reactions giving rise to asymmetric atoms—the bromination of stilbene and the hydrogenation of benzoylformic acid. The attempts made by other investigators who tried to effect asymmetric syntheses in the plane-polarized light also failed.

Had these scientists been more attentive to the publications of physicists, they would have known that their attempts were doomed to failure because the physical effects used by them were not asymmetric: in 1894 Pierre Curie indicated that asymmetric physical agents were *circularly* polarized light and also the light radiation that spread in parallel to the force lines of the magnetic field.

The first successful asymmetric syntheses under the action of circularly polarized light were carried out at the beginning of this century; this has already been mentioned in the section devoted to asymmetric syntheses (see page 151). At this point we are interested in a different aspect of the problem: Could such processes be effected under natural conditions?

There is circularly polarized light on Earth: this is the moonlight or the light reflected from the sea surface; a certain predominance of the *right* component has been noted. One can visualize that the naturally occurring circularly polarized light encountered in nature was the cause of primary asymmetry. In laboratory conditions, the effect is insignificant during short periods of time, but there might have been accumulated a very large amount of various optically active substances in nature for millions of years. Besides, under the conditions of the formation of liquid crystals there can be produced a very powerful beam of circularly polarized light, as has been demonstrated in the experiments carried out by Robinson (38).

Another currently known route for absolute asymmetric synthesis is by carrying out catalytic reactions on optically active quartz (see page 150). There are data indicating the preferential adsorption of one of the optical antipodes of the cobalt complex of ethylenediamine and amino acids on optically active powdered quartz. Akabori (39) postulated the participation of the asymmetric surfaces of mineral catalysts in the possible formation of chiral polypeptides from formaldehyde, ammonia, and hydrocyanic acid (40), though optical activity could not be detected experimentally in the syntheses accomplished.

A further supposed route to the origin of optically active organic substances is the possible occurrence under natural conditions of processes of resolution of racemates. For example, one can visualize the occurrence of the processes of spontaneous crystallization of one of the antipodes or the formation of inclusion compounds with optically inactive substances (say, with urea).

Of interest is the report that appeared in 1968, in which it was indicated that under the influence of the bremsstrahlung radiation of radioactive strontium D-tyrosine breaks down more rapidly than L-tyrosine (41). If this observation is confirmed, it will account for the fact that the proteins contained in living organisms on Earth are composed just of L-amino acids.

As early as 1932, in connection with a discussion of the problem of the origin of the first optically active organic substances, Mills noted that racemic nature is a static concept. As a matter of fact, the smaller the number of molecules with an asymmetric carbon atom formed, the greater the probability of the L/D ratio being different from unity. A model proof of the validity of this statement is provided by the results of the experiments on the crystallization of sodium chlorate, which were carried out in 1898 by Kipping and Pope. This compound can form right- or left-handed crystals, but of the 46 experiments conducted only in two experiments was the racemic conglomerate formed (50 per cent of right-handed crystals and 50 per cent of left-handed crystals); in the other 44 experiments the fraction of (+)-crystals varied from 24 to 77 per cent. The average population of (+)-crystals in all the 46 experiments was $50.08 \pm 0.11$ per cent, i.e., corresponded exactly to the racemic ratio. Thus, on formation of a small number of molecules that subsequently entered into the composition of living matter, the predominance of one of the antipode forms could have been expected, with the subsequent fixation and increase of this prevalence in the process of further chemical and biochemical transformations.

The Mills' idea brought up to its logical end is interpreted by a number of authors as the conception that the entire biological evolution is based on a *single* chiral molecule. Such a molecule must have been either a (+)- or (—)-antipode, and as a result of its transformations there supposedly originated the entire organic kingdom on Earth. In spite of its logic, this reasoning has nonetheless a theologic tinge: not without reason, the author of one of the articles (42) used the expression "molecular Adam" in this connection, implying the replacement of God by a single molecule that created the whole world.

Alpatov (43) has made an attempt to relate the asymmetry of *organisms* (the direction of the spirals of colonies of bacteria, of mussel whorls, etc.) to the possible asymmetry of the constituents of living organisms. However, no differences in the amino-acid composition of

the right- and left-handed forms of the mollusk *Fruticicola lantzi* could be detected. Stereospecificity has been revealed in a study of the action of optically active mepacrine hydrochloride on a colony of the right- and left-handed forms of *Bacillus micoides:* the (—)-antipode of mepacrine hydrochloride retards the growth of colonies of the left-handed form more strongly than that of colonies of the right-handed form. In other experiments with the same bacteria it has been found that the ratio of the right- and left-handed colonies can be influenced by growing the bacteria in the presence of (+)- or (—)-tartaric acid.

Similar results have been obtained by growing the indicated bacteria in an artificial culture medium containing enantiomeric amino acids: in the presence of the L-antipodes of leucine, valine, histidine, and alanine both the right- and left-handed colonies were developing in a normal way. In the presence of the D-antipodes of the same amino acids the right-handed colonies grew better, and when D-isoleucine was added, the left-handed colonies were completely converted into right-handed ones.

To account for these observations, Gauze advanced the idea that the inversion of the colonies is associated with the inversion of some substances (not necessarily the amino acids!) in the cell protoplasm, say, with the formation of anomalous enzymes. Extending this idea further, Gauze even assumed that the unusual forms of the colonies of *Bacillus micoides* simulate, to a certain extent, the abnormal cancer cells. This assumption was based on experiments in which D-glutamic acid was isolated from cancer cells (44) or unusual stereochemical features of the blood plasma were detected in cancer-infected patients (45). The interesting biochemical problems raised in these works have unfortunately remained unsolved up to the present time.

The problems of the origin of primary optical activity were among the subjects discussed at a symposium on the origin of life on Earth (46).

To sum up, we shall formulate the concrete questions associated with the problem of primary asymmetry that must be answered:

1. How did the first optically active organic substances appear on Earth: by way of asymmetric synthesis or by way of resolution of the initially formed racemates?

2. What asymmetric agent contributed to the occurrence of an asymmetric synthesis in natural conditions?

3. Was the creation of an optically active substance a single act or was it repeated many times?

4. Could the configurations observed under the conditions existing on Earth (L-amino acids, D-sugars) be regarded as a chance event or could there exist, in principle, a planet somewhere in the Universe with life based on D-amino acids and L-sugars?

5. Did the asymmetry arise at the early stage of the chemical evolution or at a later stage, or else did it develop in the process of the primary biological evolution?

Analysing all that has been said in this section from the standpoint of providing answers to the questions, we have to conclude that, though there is at present some material allowing us to answer some of the questions, the true overall picture of the origin of optically active substances in nature cannot yet be visualized today.

In conclusion, it must be emphasized once again that what has been said above refers to the *primary origin* of optically active organic compounds in nature; their "reproduction" in living organisms with the aid of enzymes is no secret.

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CHAPTER 12

# Stereochemistry of Complex Compounds

## 12.1. GENERAL

In 1891 Werner laid the foundation of the chemistry of complex compounds in general and their stereochemistry, in particular. Werner's ideas were of the same fundamental importance in this field as the stereochemical ideas advanced by van't Hoff for stereochemistry in general. Without entering into the details of the problem of the nature of the interaction making the seemingly "valence-saturated" particles unite, the problem that had not yet been clarified at the time, Werner classified the complex compounds known in his time into a well-composed system, making use of the concept of the coordination number.

The **coordination number** of the central atom of a complex is equal to the number of atoms or monodentate (occupying a single coordination site) groups linked to it. The groups attached to the central atom are termed **ligands.**

The stereochemical characteristics of complex compounds are determined to a considerable extent by the coordination number of the central atom. Therefore, we shall consider complexes in the order of increasing coordination numbers, beginning with the simplest ones.

## 12.2. COMPLEXES WITH COORDINATION NUMBERS 2 AND 4

Complexes with a coordination number of 2, i.e., of the composition $MX_2$ or YMX, may be visualized as having either a linear or an angu-

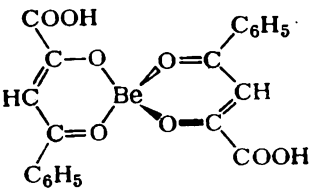
lar form. The linear structure has been detected for complexes of gold with phosphines, X—Au—$PR_3$ (X = halogen atom).

On the basis of theoretical considerations, the angular structure should be expected to exist in complexes of thallium and indium, L—Tl—X and L—In—X (L = ligand), but such complexes are not known at present.

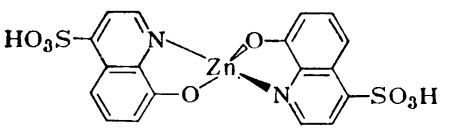
Four ligands may cluster around and combine with the central atom either tetrahedrically or in a planar fashion:

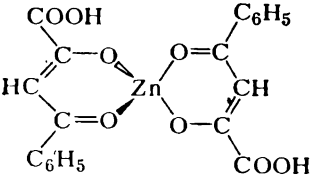
There is a third possibility—a tetragonal pyramid, but it is of no practical importance.

The stereochemical consequences of the tetrahedral arrangement are well known for carbon compounds—this is the mirror-image (optical) isomerism of compounds of the type $C^{*}abcd$. The same isomerism has been revealed in tetrahedrically built complex compounds. These include, for example, optically active borosalicylic acid which has already been encountered (see Chapter 10, page 601), the beryllium complex of benzoylpyruvic acid ester (here and further in the text we shall represent bonds in a formal way, without differentiating between the ordinary covalent and coordinate bonds):



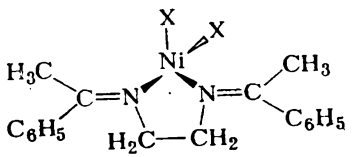

The brucine salt of this compound has been isolated in the form of two diastereomers, from which, when working rapidly, there can be prepared the antipode dimethylamine salts which are readily racemizable. The same behaviour is displayed by the tetrahedral complexes of zinc and copper; for example:



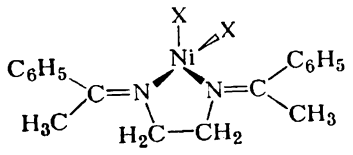



The resolution of zinc complexes into optical antipodes has been effected with the aid of alkaloids in pyridine solution.

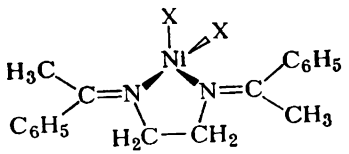
A peculiar geometrical isomerism has been detected by nuclear magnetic resonance (NMR) spectroscopy in tetrahedral complexes of nickel, those of the type $LNiX_2$ (X = halogen atoms, L = bidentate ligand, which may be a Schiff's base obtained from ethylenediamine and acetophenone) (1). Depending on the configuration at the C=N bond, there may exist three geometrically isomeric forms:



*cis-exo*

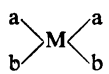


*cis-endo*

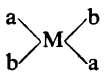


*trans-*

Another group includes planar four-coordinate complexes. Their characteristic feature is the manifestation of *cis-trans* isomerism:



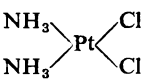
*cis*-Form



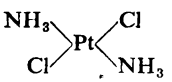
*trans*-Form

With the tetrahedral arrangement such an isomerism would be impossible.

A classical example is complexes of platinum; for example:



*cis*-Form

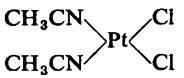


*trans*-Form

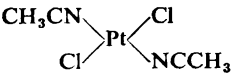
The two forms differ from each other in physical properties; in particular, the *trans*-form has a higher melting point but a lower solubility than the *cis*-form. A dipole moment is exhibited only by the *cis*-form. The chemical properties of the two forms are different too: thus, for

example, the *trans*-form instantly gives a precipitate under the action of silver nitrate, and the *cis*-form reacts much more slowly. The difference in chemical properties between such complexes has been thoroughly studied by Chernyaev. It has been found that the reactivity depends on the nature of the group opposite the reacting one: this phenomenon is known as the *trans*-effect.

There are also known planar four-coordinate complexes of platinum, which contain ligands other than ammonia; for example:

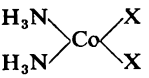


*cis*-Form

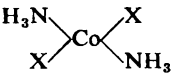


*trans*-Form

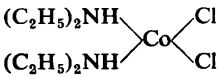
Planar four-coordinate complexes are known to exist for other metals as well; for example, those of cobalt:



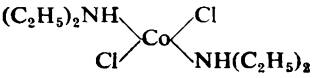
*cis*-Form



*trans*-Form

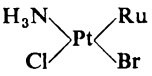


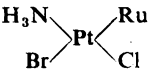
*cis*-Form

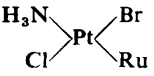


*trans*-Form

Planar complexes of the type M*(abcd)* may, in principle, have three geometrical isomers, for example:





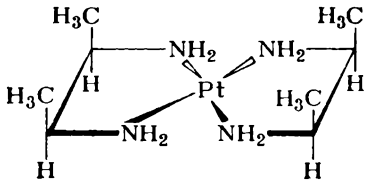


For the configuration of planar four-coordinate complexes to be determined, dipole moment measurements are especially widely used. Thus, for example, the *cis*-form of the complex $[(C_2H_5)_3P]_2PtCl_2$, which has a dipole moment of 12 D, instantly reacts with an alcoholic solution of $AgNO_3$. The *trans*-isomer of the complex, which has no dipole moment, reacts with the same reagent only in several hours. Planar four-coordinate complexes of nickel and cobalt behave analogously.

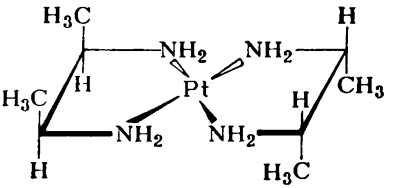
Of special stereochemical interest are complex compounds in which, with the ligands occupying two and more coordination sites (bidentate and polydentate ligands), there are formed cyclic structures containing

a metal atom. Such compounds are termed **inner-complex compounds** or **chelates**. (The word chelate is derived from the Greek, meaning a claw, as of a lobster.)

Planar chelate complexes of platinum with ligands of the type of 2,3-diaminobutane may contain substituents ($CH_3$ groups in this case) either in the *cis*- or in the *trans*-position:

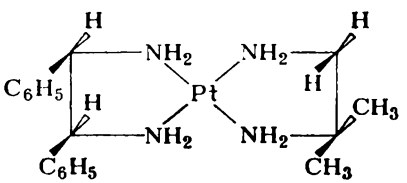


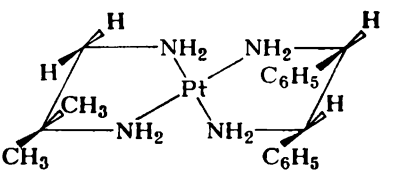

*cis-*



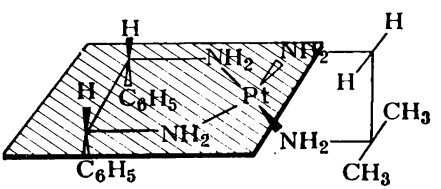

*trans-*

Ligands built up appropriately may also cause optical isomerism in planar four-coordinate complexes:



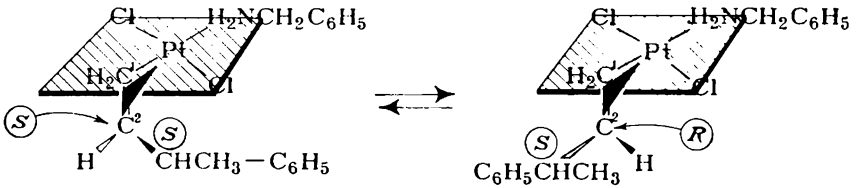




The resolution into optical antipodes in this case proves the planar configuration: with the tetrahedral configuration there would have been a plane of symmetry, as shown below:



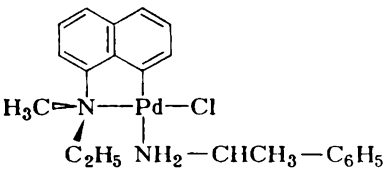

Tetradentate Schiff's bases produced from (—)-propylenediamine or (—)-cyclohexane-1,2-diamine with salicylaldehyde form planar complexes with nickel. The study of the optical dispersion of these complexes has shown that the sign of the Cotton effect depends on the conformation of the chelate ring, which is in its turn determined by the stereochemistry of the ligand (2).

Stereoisomerism also arises in planar square complexes of platinum with olefins. In the complex with optically active 3-phenylpentene shown below, the former olefinic carbon atom C-2 may, in principle, assume two configurations and two diastereomers can thus be formed. When isolated in the crystalline state, only one diastereomer can be obtained: under the influence of the chirality of the olefin a new centre appears in one configuration only (3).



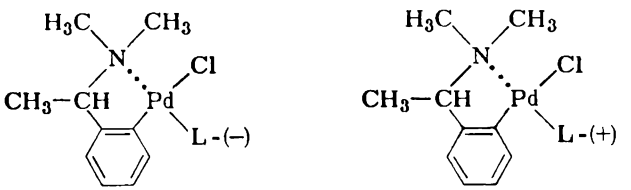

Optically active complexes of metals with olefins have also been considered by Paiaro (4).

Planar palladium complexes have found an interesting application for fixing the configurations of compounds of trivalent nitrogen. A complex of the structure




with the (—)-α-phenylethylamine residue has an NMR spectrum indicating the presence in the solution of two diastereomers; the nitrogen atom becomes the second chiral centre (5).

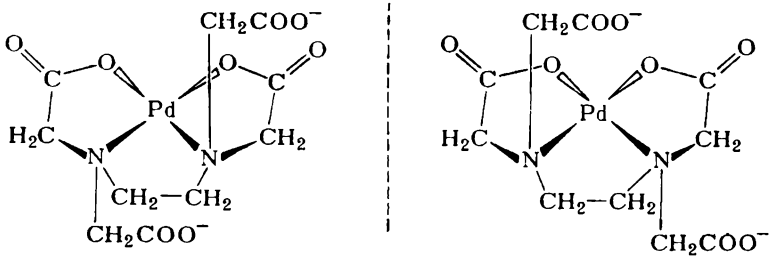
Phenyl-*o*-tolyl-α-naphthylphosphine (designated as L below) has been resolved into optical antipodes via an analogous palladium complex (6). For this purpose, phenyl-*o*-tolyl-α-naphthylphosphine was converted into a diastereomeric complex:



After the diastereomers were separated they were decomposed and the optically active phosphine L isolated.

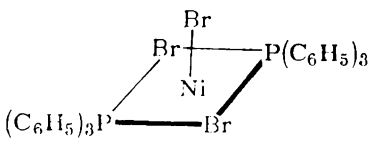
The resolution of a complex of zinc with 8-hydroxyquinoline-5-sulphonic acid into optical antipodes has also been described (7).

Ethylenediaminetetraacetic acid, functioning as a tetradentate ligand, forms a planar complex with divalent palladium. This complex is chiralic and may exist as a pair of optical antipodes:



## 12.3. COMPLEXES WITH COORDINATION NUMBER 5

Complexes with a coordination number of 5 are encountered relatively seldom. Trivalent nickel is known to form such a complex with a phosphine, $NiBr_3 \cdot 2P(C_2H_5)_3$. It is built as a square pyramid (8):



Complexes of divalent cobalt and nickel with "trias" are believed to have an analogous structure:

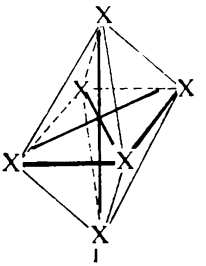
$NiBr_2 \cdot trias$ $\qquad$ $CoI_2 \cdot trias$

$trias = CH_3As[CH_2CH_2CH_2As(CH_3)_2]_2$

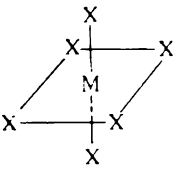
## 12.4. COMPLEXES WITH COORDINATION NUMBER 6

Complexes with a coordination number of 6 are the most numerous and the most thoroughly studied. They exist in the octahedral configuration

(I) which is usually represented schematically as (II):



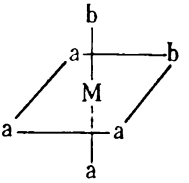
I



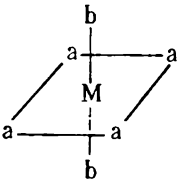
II

All the six positions of the octahedron are equivalent, though from the conventional drawing it does not seem to be the case. Certain types of octahedral complexes may exhibit *cis-trans* isomerism; for example:

Complexes of the type $M(a_4b_2)$

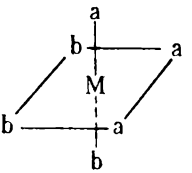


*cis*-Form

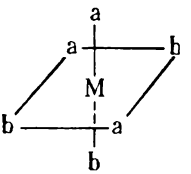


*trans*-Form

Complexes of the type $M(a_3b_3)$



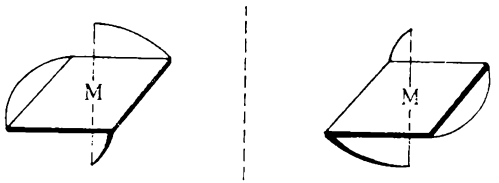
*cis*-Form



*trans*-Form

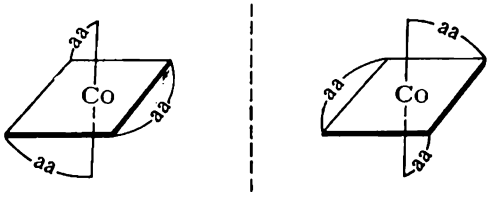
Geometric considerations indicate that complexes of the type $M(a_2b_2c_2)$ may have five geometrical isomers, one of them being chiralic and capable of existing as a pair of optical antipodes. However, for complexes containing only monodentate ligands, no optical antipodes are known to exist. On the contrary, there have been obtained various optically active complexes of the chelate type (with ligands occupying two and more coordination spaces). This especially refers to complexes with

bidentate ligands:




Complexes of this type are formed by trivalent cobalt with ethylenediamine, and trivalent nickel with dipyridyl. An important achievement in this field is the X-ray determination of the absolute configuration of the tris(ethylenediamine)-cobalt ion, which has been carried out by Saito *et al.* (9).

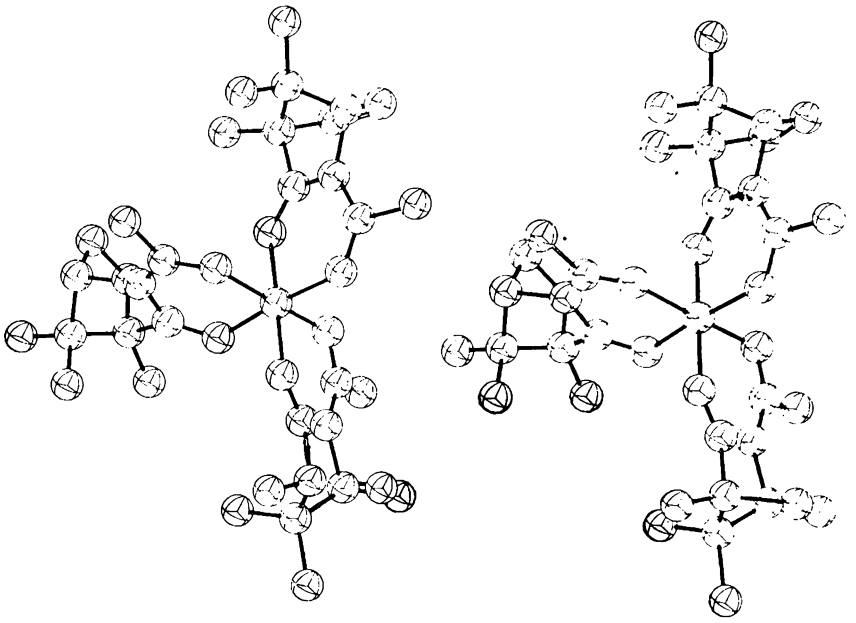
An example of non-ionic compounds of this type is furnished by complexes of trivalent metals with acetylacetone (designated below as aa) of the composition $M(aa)_3$. The acetylacetonate complexes of trivalent cobalt and chromium have been resolved into optical antipodes by the adsorption method on sorbite or mannite.




In spite of the fact that high optical purity could not be achieved by resolution, rotations of hundreds of degrees were revealed since the specific rotation of these complexes is very great (10). In a similar way (11), by means of chromatography on D-(+)-lactose, chromium, cobalt, ruthenium and rhodium tris-acetylacetonates have been partially resolved into optical antipodes. A complex of trivalent chromium with hexafluoroacetylacetone has been obtained in an optically active form by means of resolution with the aid of gas-liquid chromatography on optically active quartz.

For the acetylacetonates of trivalent chromium and trivalent cobalt to be resolved into optical antipodes, use was also made of aluminium oxide which after being treated with (+)-tartaric acid assumed the properties of an asymmetric adsorbent (12).

Figure 12.1.



*The three-dimensional structure of tris-α-diketonic complex of trivalent chromium (the ligand used is (+)-acetylcamphor).*

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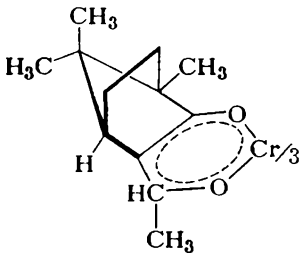
The X-ray diffraction analysis has been used to determine the absolute configuration of tris-β-diketonic complex of trivalent chromium with (+)-acetylcamphor as the ligand (13):



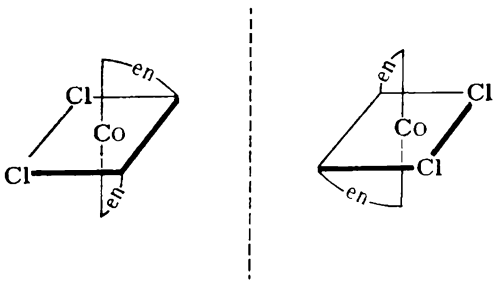

This publication is also interesting in that the configuration is given as a stereopair (Fig. 12.1) to be viewed under the stereoscope.

---

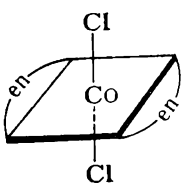
Even more complex is the isomerism of complexes with unsymmetrical dicarbonyl compounds. As an example may be cited the tris-benzoylacetonate of trivalent chromium, which can exist as four chiral isomers (the tris-benzoylacetonate is represented conventionally) (14):

Optically active tris-acetylacetonates of chromium, cobalt, and rhodium enter into electrophilic substitution reactions: chlorination, bromination, nitration. In these reactions, the chelate ring behaves as an aromatic system. Optical activity is retained in these transformations.

Chirality is also exhibited by octahedral complexes with two bidentate ligands. An example is the complex $[Co(en)_2Cl_2]X$, the central ion of which has the following structure (here and afterwards "en" denotes the ethylenediamine residue):



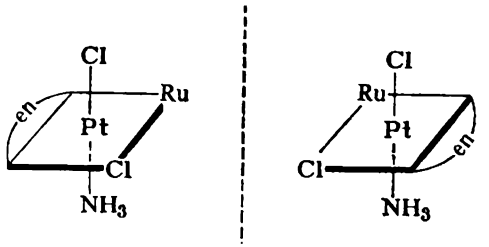

The possible spatial isomerism of this compound is not, however, exhausted by the existence of two optical antipodes. Optical activity is characteristic here of one of the geometrical isomers, which is called the *cis*-form (the two monodentate ligands are close together). Besides, there also exists the *trans*-isomer (the term is used according to the *trans*-position of pairs of identical ligands) which is incapable of resolution into optical antipodes and which differs from the *cis*-isomer in physical constants:



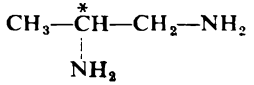
Two geometrical isomers, the *cis*- and the *trans*-form, the first of which can be resolved into optical antipodes, exist also for complexes of the type $M(LL)_2XY$, where LL is a bidentate ligand and X and Y are monodentate ligands. As an example may be cited the stereoisomeric complexes obtained by Werner in 1911:

$$(H_2NCH_2CH_2NH_2)_2Co(NH_3)Cl$$

Finally, even one bidentate ligand with an appropriate set of monodentate ligands can create chirality in a complex; for example (15):




If, instead of symmetrical ethylenediamine, the octahedral *tris*-complex contains 1,2-propylenediamine

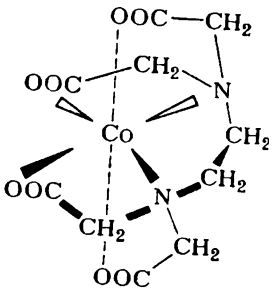


(it is designated as "pn"), which itself can exist as a pair of optical antipodes, then the complex $Co(pn)_3^{3+}$, with account taken of the configuration of the central metal atom, can exist as eight diastereomers. If we designate the configuration of the central atom by the letters *D* and *L* and the configuration of propylenediamine by *l* and *d*, the following combinations will be obtained:

| | |
|---|---|
| $Dl_3$ | $Ld_3$ |
| $Dl_2d_1$ | $Ld_2l_1$ |
| $Dl_1d_2$ | $Ld_1l_2$ |
| $Dd_3$ | $Ll_3$ |

The stability and, accordingly, the rate of formation of the diastereomers are not the same—the complex $Dl_3$ is the preferred one.

In complexes with trivalent cobalt, ethylenediaminetetraacetic acid is a hexadentate ligand. The structure of the resulting complex is chiralic; it has been resolved into optical antipodes (16).



## 12.5. THE NATURE OF OPTICAL ACTIVITY OF COMPLEX COMPOUNDS

The use of the spectropolarimetric method—the study of optical rotatory dispersion (ORD) and circular dichroism (CD) curves—has enabled a deeper understanding of the nature of the optical activity of complex compounds.

Recall that a comparison of the spectral position of the Cotton effect (or the circular dichroism bands) with the absorption bands of the chromophores present in the molecule may lead one to draw conclusions as to which of the specific features of the molecular structure are responsible for the creation of optical activity.

In the case of complex compounds, the most informative is the study of the spectral region covering the $d - d$ transitions of the metal. Compounds of such metals as copper, cobalt, nickel, iron, chromium, have absorption bands associated with $d - d$ transitions in the visible region of the spectrum convenient for measurements. Therefore, the ORD curves of such complexes had been examined long before the advent of modern ultraviolet spectropolarimeters.

It was originally assumed that the Cotton effect in the *d,d*-region appeared only in chelates (17). Later it was found out, however, that the Cotton effect could be observed in complexes of the non-chelate type as well, though its magnitude is, as a rule, much lower than in chelates. Fujita and coworkers (18) have shown this to be the case by comparing the Cotton effect of two types of compounds: the chelates $[Co(NH_3)_4 \cdot$L-amino acid$]^{2+}$, in which the amino acid plays the role of a bidentate ligand, and the non-chelate complexes $[Co(NH_3)_5 \cdot$L-amino acid$]^{3+}$, in which the amino acid is a monodentate ligand.

Even more convincing is the investigation showing the presence of a Cotton effect in the region of $d$—$d$ transitions of palladium in complexes of di- and tetravalent palladium with (—)-α-phenylethylamine: for *trans*-$[PdCl_2(amine)_2]$ and *trans*-$[PdCl_4(Amine)_2]$.

In tetrahedral and octahedral complexes, the metal atom itself may be the chiral centre. In such cases, the amplitude of the Cotton effect in the region of $d$ — $d$ transitions of the metal is especially high since the metal plays the role of both the chromophore and the chiral centre. The magnitude of the Cotton effect depends, in the long run, on the nature of the ligands creating the chiral environment, and the sign of the Cotton effect is directly associated with the configuration around the central atom. The optical activity created in this way is called the **configurational optical activity.**

The optical activity in the region of $d$ — $d$ transitions may also be a consequence of the **vicinal effect** of the asymmetric centres of an optically active ligand on the central metal atom. Since this effect reaches the chromophore via several atoms, it becomes weakened and the magnitude of the Cotton effect in this case is lower than that of the configurational effect.

If complex formation gives rise to *non-planar* metallocycles, then an additional contribution, a **conformational** one, arises as a consequence of the asymmetry of these metallocycles.

Thus, the actually observed optical rotation is the sum of three contributions: configurational, vicinal, and conformational. By studying the ORD or CD curves of a series of related compounds, it is possible to obtain data in order to separate each of these contributions from the observed rotation through calculations. This has been done, for example, by Douglas (19) for cobalt complexes with ethylenediamine and propylenediamine.

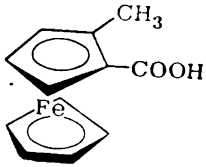
A knowledge of the components provides much more information than the knowledge of the total rotation. Thus, the determination of the configuration around the central metal atom by the method of comparing the ORD or CD curves of the complex under study with the corresponding curves of the complexes, the configurations of which have been reliably established (for example, by means of the X-ray diffraction method), will be more rigorous if the configurational contributions rather than the total curves are compared. The vicinal contribution is useful in the determination of the absolute configuration of a chiral ligand. The conformational contribution affords information on the spatial structure of the chelate ring, on whether it is planar or distorted.

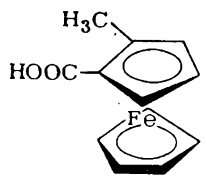
The optical activity of transition-metal complexes has also been studied by a number of authors (20).

## 12.6. METALLOCENES AND RELATED COMPOUNDS

Peculiar stereochemical relationships are observed in ferrocene and related compounds (for a review, see ref. 21).

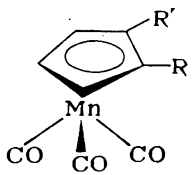
Any derivative of ferrocene that contains at least two non-identical substituents in one of the rings is devoid of the elements of symmetry and, hence, is capable of existence in an optically active form; for example:

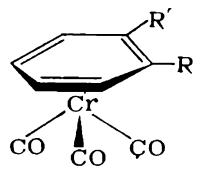


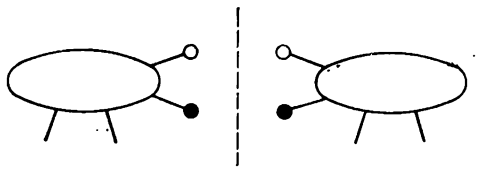

Schlögl has not only obtained a wide range of such optically active compounds but also studied their optical rotatory dispersion and circular dichroism and determined the absolute configuration.

Optically active derivatives of cyclopentadienylmanganese tricarbonyl (cymanthrene) and also of benzenechromium tricarbonyl and ruthenocene belong to the same class of compounds.




The substituents in all these compounds lie in the plane of the ring. It is well known that in analogous planar systems — olefins and benzene derivatives, no asymmetry is present. But why does it arise in metallocenes? The geometrical reason is that metallocenes are structures with their top and bottom parts being different. This may be shown by means of the following simplest scheme:

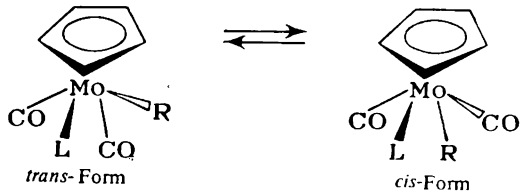


The asymmetry here is the same as it could have been with a beetle, having different rather than identical feelers.

These compounds are all examples of optically active compounds with a plane of chirality.

The derivatives of cyclopentadienylmolybdenum have been found to

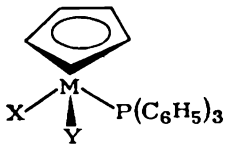
be capable of existence in peculiar geometrically isomeric forms (22).




R = H, D, $CH_3$, $CH_2C_6H_5$, Cl, Br, I;
L = $P(C_6H_5)_3$ and analogous compounds

The energy barrier separating such *cis-trans* isomers ranges from 50 to 110 kJ/mole according to NMR spectral data.

By varying the substituents in complexes of the type under consideration it is possible to arrive, in the long run, at compounds with asymmetry being due to the central transition-metal atom itself; for example:




M = Cr, Mo, W;
X = CO, NO;
Y = CO, COOR, $CH_3CO$

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